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THE SPLEEN IN HODGKIN'S DISEASE, LYMPHOSARCOMATOSIS AND LEUKEMIA. By PAUL KLEMPERER, M.D. 593

IS TYPICAL HODGKIN'S DISEASE AN INFECTION OR A NEOPLASM? By E. B. KRUMBHAAR, M.D. 597

THE DIFFERENTIAL DIAGNOSIS OF AGRANULOCYTIC ANGINA FROM ACUTE LEUKEMIA. By HENRY JACKSON, JR., M.D. 604

FIVE-YEAR SURVIVAL IN HODGKIN'S DISEASE. By LLOYD F. CRAVE[illegible] M.D. . . 609

IRRADIATION IN LYMPHOSARCOMA, HODGKIN'S DISEASE AND LEUKEMIA (A STATISTICAL ANALYSIS). By T. LEUCUTIA, M.D. 612

THE SYNDROME OF ACUTE AGRANULOCYTOSIS AND ITS OCCURRENCE AS A COMPLICATION OF KALA-AZAR. By LILY S. ZIA, M.D., and CLAUDE E. FORKNER, M.D. . 624

HEART DISEASE IN THE MIDDLE WEST. (INCIDENCE AND ETIOLOGY OF 1646 CASES AT THE COOK COUNTY HOSPITAL.) By NATHAN FLAXMAN, M.D. . . . 639

A STANDARDIZED EXERCISE TOLERANCE TEST FOR PATIENTS WITH ANGINA PECTORIS ON EXERTION. By JOSEPH E. F. RIESMAN and BEATRICE STERN . . . 646

WHAT TREATMENT IN EARLY SYPHILIS ACCOMPLISHES
I. RELAPSE AND "CURATIVE" RESULTS 660
II. OPTIMUM TREATMENT 669
III. COMPARISON OF BRUUSGAARD'S WORK AND THE 3- TO 20-YEAR RESULTS OF THE CO-OPERATIVE CLINICAL GROUP. By JOHN H. STOKES, M.D., with LIDA J. USILTON, M.A., and HAROLD N. COLE, M.D., JOSEPH EARLE MOORE, M.D., PAUL A. O'LEARY, M.D., UDO J. WILE, M.D., THOMAS PARRAN, JR., M.D., JOHN McMULLEN, M.D. 678

THE RELATIONSHIP BETWEEN ANTISYPHILITIC TREATMENT AND TOXIC CIRRHOSIS. By C. W. BALDRIDGE, M.D. 685

RECURRENT LARYNGEAL PARALYSIS IN LEFT VENTRICULAR FAILURE. By FREDERICK H. KING, M.D., WILLIAM M. HITZIG, M.D., and ARTHUR M. FISHBERG, M.D. . 691

LIMITATIONS OF AUSCULTATION FOR THE DIAGNOSIS AND STUDY OF TUBERCULOUS PULMONARY CAVITIES. By B. T. McMAHON, M.D., and EDMUND H. KERPER, M.D. 697

SOME EFFECTS OF QUININ DERIVATIVES IN EXPERIMENTAL PNEUMOCOCCUS STUDIES. By W. W. G. MACLACHLAN, M.D., H. H. PERMAR, M.D., JOHN M. JOHNSTON, A.B., M.D., and JOSEPH R. KENNEY, A.B., B.S., M.D. 699

THE DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE OF THE CREATIN-CREATININ METABOLISM IN VARIOUS MYOPATHIES BEFORE AND AFTER AMINO-ACID THERAPY. By HOWARD H. BEARD, M.A., PH.D., CARLO J. TRIPOLI, M.D., and JEROME E. ANDES, PH.D. 706

ARTERIOLAR ESSENTIAL HYPERTENSION AND ACTIVE TUBERCULOSIS: THEIR RARE ASSOCIATION. By DAVID AYMAN, M.D. 712

DELAYED RESOLUTION IN LOBAR PNEUMONIA AND ITS RELATIONSHIP TO PRE-EXISTING SYPHILIS. By ALBERT WEINSTEIN, M.D., and MORTON GOODMAN, M.D. 716

INDEX TO PHYSICIAN'S SUPPLIES ADV. PAGE 34

Contents continued on adv. page 10

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AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

NOVEMBER, 1934

ORIGINAL ARTICLES.

THE SPLEEN IN HODGKIN'S DISEASE, LYMPHOSARCOMATOSIS AND LEUKEMIA.*

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In the differential diagnosis of diseases of the hematopoietic system the spleen justly receives a great share of attention. The relative size of the spleen is of comparatively little diagnostic value in the differentiation between lymphadenosis and myelosis, although it is true that the average weight is far greater in the myeloid type of hyperplasia. Individual cases of leukemic or aleukemic lymphadenosis, however, not infrequently present great degrees of splenomegaly. Enlargement is valuable for the differential diagnosis between aleukemic hyperplasia (true pseudoleukemia) and those atypical, more neoplastic proliferations of the lymphatic and myeloid system, such as lymphosarcomatosis, which also run aleukemic courses. The spleen in lymphadenosis, as a rule, presents a diffuse infiltration of hematic cells; for this reason cut surfaces of the organ likewise differ from those found in lymphosarcomatosis. In lymphosarcomatosis, if the spleen is affected, it is mottled by scattered circumscribed nodules up to hazelnut size. These lesions are regarded as hematogenous metastases. Their sharp definition and striking white color differentiate them from the splenic infiltration

* This and the following 4 papers formed part of a round table conference on certain diseases of the hematopoietic system, held at the Memorial Hospital, in connection with its fiftieth anniversary celebration, May 25, 1934. The fifth paper of the symposium, by Dr. Elise S. L'Esperance on "Role of the Tubercle Bacillus in Hodgkin's Disease, Lymphosarcoma and Leukemia," will be published later.

of Hodgkin's disease. The well-known porphyry spleen is often a useful touchstone for the recognition of Hodgkin's disease in the gross, yet it should be remembered that in some cases of the disease the spleen may escape involvement entirely or may even present a diffuse enlargement which is neither macroscopically nor microscopically typical.

The microscopic appearance of the spleen generally conforms to the macroscopic. The detailed histologic characteristics of the different forms are no doubt well known to everyone present today. It is not amiss to mention, however, that the cellular infiltrations of myeloid leukemia may consist of other bone marrow cells as well as myelocytes and their precursors. In rare instances there are large numbers of megakaryocytes and erythroblasts. The differential diagnosis between *lymphatic* and *micromyeloblastic* leukemia may likewise cause difficulty. The clarification of such cases usually depends on detailed cytologic investigations, preferably of splenic spreads. In acute leukemia, especially in infancy, the immaturity of the infiltrating cells may make classification impossible. The topographic distribution of the cells may likewise fail as a criterion, since the Malpighian corpuscles—the chief landmark—are often obliterated. Cases of this sort are best designated *hemocytoblastic* or *stem cell leukemia*.

The classical publications of Drexler, Kundrat, Sternberg, and Reed seemed to have classified the generalized diseases of the hematopoietic mesenchyme for all eternity. But the years have brought increasing numbers of atypical cases, and at the present time even such authoritative pathologists as Mallory and Warthin would abandon the rigid classifications of our predecessors. The unitarian view now demands serious consideration. The clue is possibly in the spleen and I shall, therefore, invite you to consider first the relative positions of lymphadenosis and lymphosarcomatosis.

This question is not a new one. Without discussing in detail the neoplastic aspect of leukemia, it may be sufficient to repeat that recent experiments suggest a close genetic relation between leukemia and lymphosarcomatosis. For human pathology the term leukosarcomatosis was devised by Sternberg to segregate those cases which manifest a marked aggressive tendency of the cellular proliferation in addition to a leukemic picture. Although this nomenclature might seem to imply a relation of leukemia and lymphosarcomatosis, Sternberg actually emphasized a strict separation of these disease groups. Kundrat, however, had observed the transformation of aleukemic lymphadenosis into lymphosarcomatosis.

Another link between lymphadenosis and lymphosarcomatosis is supplied by the cases of giant follicular hyperplasia of the lymph nodes and spleen, originally described by Brill, Rosenthal and Baehr.[1] While early phases here resemble aleukemic lymph-

adenosis, necropsy years later presents evidence of tumor formation of lymph nodes and invasion of neighboring structures, precisely as in lymphosarcomatosis.[2] In only a few cases was the spleen examined during the early hyperplastic phase of the process. The organ was greatly enlarged, the cut surface was dotted with innumerable nodules composed of small and large lymphocytes around the follicular arteries and their ramifications. This appearance differs from the familiar diffuse splenic infiltrations of lymphatic leukemia, yet it is not rare in that dyscrasia (Bezançon,[3] Lubarsch, Figs. 136 and 138[4]). It is interesting that 1 of the cases of follicular lymphoblastoma developed a blood picture characteristic of chronic lymphatic leukemia. At necropsy the spleen showed the appearance which I have just described. All of the lymph nodes were found to be enlarged. They were discrete except in the pancreatic region where infiltration of the capsule and adjacent areolar tissue was noted. In the other autopsied cases splenomegaly gradually disappeared before the fatal term of the disease. Microscopic examination, however, showed that the Malpighian corpuscles were large and that considerable cell atypism was still present. In other respects, it may be reiterated, these latter cases conformed to the anatomic picture of lymphosarcomatosis because of conspicuous aggressive tumor formation of the lymph nodes with infiltration of the neighboring organs. These observations suggest that the follicular lymphoblastoma represents a definite link between lymphadenosis and lymphosarcomatosis. In the early stages of its evolution the process is merely hyperplastic, while in the later stages it becomes atypical and aggressive.

In classic lymphosarcomatosis, moreover, 2 cases of a series of 16 showed enlarged Malpighian corpuscles composed of atypical lymphoblasts with hyperchromatic nuclei.

All such experiences point to a close affinity between the *simple hyperplastic* and the *neoplastic* proliferations of the lymphatic system. This is evident even in the spleen, the appearance of which has hitherto constituted one of the chief reasons for strict separation. It is necessary to state, however, that the *generalization* of the cellular proliferation militates against the rigid identification of either lymphadenosis or lymphosarcomatosis with the malignant neoplasms. Orth's term, *hemoblastosis*, implying unlimited hematic cell proliferation, might serve to encompass lymphadenosis and lymphosarcomatosis in a single domain.

The coördination of these morbid processes simplifies the comparison with Hodgkin's disease. A number of eminent pathologists include all 3 under a single category, basing this concept largely on microscopic evidence. This tends to undervalue the macroscopic evidence, and I, therefore, dissent from this belief. In my own opinion the evaluation of an individual case is greatly dependent on the gross appearance of the spleen. Whenever the spleen is

involved in Hodgkin's disease the alteration is macroscopically characteristic and can easily be differentiated from the splenic lesions observed in the hemoblastoses. Those splenomegalies of Hodgkin's disease which are not characteristic, such as described by Jona and Torre,[5] which I have twice been able to verify, may be grossly indistinguishable from the enlargement in the hemoblastoses; but microscopic differentiation is assisted by the absence of hematic cell infiltration. The identification has been proposed not only because of clinical analogies but also because of an alleged transition from one type into the other. This transition is supposedly proved by changes found in repeated biopsies. Such proof loses validity when one recognizes that several lymph nodes removed *simultaneously* may often exhibit wide histologic variation. Moreover, *in a single biopsy* it is not rare to encounter insurmountable difficulties in the differential diagnosis between reticulum cell sarcoma and the monotypic forms of Hodgkin's disease. Such cases are clarified only at necropsy, and the gross appearance of the spleen is sometimes decisive in the final diagnosis. In a previous publication[6] I have set forth the reasons why I believe that Hodgkin's disease is essentially a granulomatous process. Today I shall only repeat that in both macroscopic and microscopic features the spleen of Hodgkin's disease differs fundamentally from those of the hemoblastoses.

Finally, I should like to refer briefly to the spleen in the so-called *reticulosis*. This term refers to those cases in which the entire hematopoietic system is involved by proliferation of large cell forms of reticulo-endothelial origin. The systematized lipoid histiocytoses (Gaucher's and Niemann-Pick's diseases) are related, but because of their chemical characterization are not included. The concept of reticulosis is not yet sharply delimited, and cases of apparently diverse pathogenesis have been included. For this reason the appearance of the spleen has not been found constant, both nodular and diffuse infiltrations having been described. Only a few of the cases have presented a proliferation of cells in reticular arrangement corresponding to the type of embryonal reticular mesenchyme and only such cases should be dignified with the title of reticulosis.

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IS TYPICAL HODGKIN'S DISEASE AN INFECTION OR A NEOPLASM?*

By E. B Krumbhaar, M.D.,
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The most important views as to the nature of Hodgkin's disease are that it is either: (1) An infection of unknown nature (lymphogranuloma) (German school, Longcope,† MacCallum, Symmers, etc.); (2) an atypical form of tuberculosis (Sternberg, l'Esperance); (3) a lymphoblastoma (Mallory, Warthin); (4) a megakaryocytoma (Medlar); (5) a disease intermediate between infection and neoplasm (Lubarsch, Levin). The proper nosologic position of Hodgkin's disease is far from being, as some would have it, an almost wholly academic question. The direction of further study, with eventual practical matters of diagnostic and therapeutic importance obviously are largely conditioned by one's attitude to such nosologic aspects.

Since Hodgkin's description, 102 years ago, of a disease with lesions in the "absorbent glands" (lymph nodes) and spleen that has since come to bear his name, the landmarks as to concepts of the nature of the disease may be roughly outlined as follows: Hodgkin himself paid little attention to its nature, other than to reject the idea of an acute inflammation. In fact, it is generally accepted that of his 7 cases at least 3 represented other diseases of the lymphoid apparatus (tuberculosis, syphilis and leukemia). In 1864, Virchow[1] included Hodgkin's and Wilk's meagerly described group with lymphosarcoma—a nosologic beginning which has overinfluenced future developments. One has but to read Virchow's masterly pioneer lecture to realize that this particular statement should carry no weight today in a consideration of the nature of Hodgkin's disease. After Virchow's and Bennett's[2] isolation of leukemia in 1845, Cohnheim assembled similar enlargements of lymph nodes without the leukemic blood picture into the group, "pseudoleukemia." Hodgkin's disease, like lymphosarcoma, fell into this group, without concern about its etiology; and it was not until 1893 that Kundrat[3] segregated the now familiar lymphosarcoma in a distinctly different sense than the term Hodgkin's disease conveyed. Desirable at one stage of progress, like "splenic anemia" in another field, Cohnheim's term "pseudoleukemia" seems now to have about reached the limit of its usefulness and be ready for the discard.

* Also presented at the Section of Pathology of the Am. Med Assn., Cleveland, June 11.

† As references to the extensive literature on Hodgkin's disease are easily available in the summaries by Simonds[5] and Wallhauser,[6] many are not repeated here.

Toward the turn of the century, two contributions were made that continue to influence two of the chief schools of thought in this problem. In 1898, Sternberg[4] regarded the condition as a peculiar form of tuberculosis, a view that has steadily found adherents and recently been supported by l'Esperance's[15] production of a Hodgkin-like process with avian tubercle bacilli from Hodgkin's material. Wallhauser[6] has listed 27 points of possible relationship between Hodgkin's disease and tuberculosis.

Sternberg[7] also began the delineation of a characteristic histologic appearance, which, furthered by the descriptions of Reed,[8] Andrewes,[9] Longcope[10] and others, has given at least one firm basis for classification. This picture is so well known that one need only refer to the main features of "endothelioid" cell hyperplasia, with characteristic Sternberg-Reed (and occasionally) Langhans giant cells, frequent eosinophils and other infiltrating cells replacing the normal lymphoid structure, with progressive fibrosis and often varying degrees of necrosis. If, as Warthin, who later became one of the chief advocates of the neoplastic theory, originally suggested,[11] "it would appear wisest to limit the pathologic diagnosis of Hodgkin's disease to the chronic inflammatory type of Reed, Longcope, etc., until its etiologic nature is discovered," then much confusion would have been avoided. Unfortunately, however, there has never been agreement on this point, and it must be admitted that many cases clinically diagnosed as Hodgkin's disease fail to give this picture. With biopsy material so easily available, and the increasing use of the biopsy method, it would seem obvious that the histopathologic report, unquestionably the most concise evidence available, should be made a paramount item in the clinical diagnosis, and only those cases diagnosed as Hodgkin's disease that conform to the histopathologic requirements. Insistence on this point—of Hodgkin's disease as a *pathologic* concept—would *ipso facto* eliminate the confusion of including a variety of conditions under the term because they happened to have similar or indistinguishable clinical pictures. Occasional splenic, abdominal and other forms might, to be sure, remain during life or even permanently undiagnosed, but even this is both scientifically and practically preferable to the present loose method of using the term now as a clinical and now as a pathologic diagnosis. In this connection, too, the dangers of such diagnoses as "atypical Hodgkin's disease" must be recognized, if we wish to avoid a morass like that of pseudoleukemia. Substitution of the word "doubtful" would often be as useful and always less confusing.

On this histopathologic basis I have examined the tissues of all fatal cases diagnosed as Hodgkin's disease in our department. Of the 40 so listed, 7 can be rejected as not meeting the histologic requirements (either obviously pure tuberculosis, blastomycosis or without sufficient data). Of the 33 remaining, none revealed a

demonstrated progress from the granulomatous to the sarcomatous picture of Hodgkin's disease—Ewing's Hodgkin's sarcoma. In 3 there was strong probability that the condition was sarcomatous from the beginning or reasonable doubt as to whether Hodgkin's disease or lymphosarcoma in one or other form was under consideration. If any of the 3 were the latter, however, the evidence for a previous Reed-Longcope histologic picture was never at hand. In the 33 cases there were 22 males, 11 females; the average age was 46, with extremes of 18 and 72 years. Evidence for an associated active tuberculosis was present in 3 cases, but may well have been overlooked in others. There were, of course, others with healed lesions, pleural adhesions or apical scars, but it was not believed that the autopsy records were sufficiently detailed to make an analysis of this item worth while. In 3 cases obviously careful study had excluded tuberculosis, as far as possible, once including bacteriologic and inoculation studies.

In other words, this material lends no support for the primary neoplastic nature of Hodgkin's disease, unimpressive evidence in favor of a causative relationship of tuberculosis and no examples of progress from the granulomatous to the neoplastic type of Hodgkin's lesion. It brings us definitely back to the probable basis of a granulomatous infection of unknown etiology.

Let us now review the accumulated evidence bearing on the infectious *versus* the neoplastic origin of Hodgkin's disease, granting that it must be regarded as indicative rather than conclusive:

1. *Histologic Picture.* Whether in lymph node (on which earlier studies were made), spleen, bone marrow or elsewhere, the histologic picture, especially in the early stages (an increase of the "endothelioid" cells of pulp and follicles, together with lymphocytes, eosinophils—first noted by Goldman—neutrophils and plasma cells), is characteristic of chronic inflammation, but would be unique for neoplasm, even a neoplasm of the reticuloendothelial system. The great increase of eosinophils in a considerable number of cases in the tissue and perhaps also in the blood is again a picture unknown in neoplasms but not uncommon in parasitic and other chronic infections, allergy, etc. As the process progresses, the characteristic "Sternberg-Reed giant cell" becomes more prominent, suggestive in different form of such infections as syphilis and tuberculosis, especially as these cells sometimes resemble the Langhans type. Pullinger[12] and Haythorn have emphasized the probable origin of these cells from the reticuloendothelial system, and Foot has pointed out that the reticulum formation suggests that of an inflammatory process. Of course, on the other hand, admixtures of giant cells in sarcoma are not uncommon. The rôle of this cell in Medlar's megakaryocytoma theory will be discussed later. The suggestion, seldom made, that the endothelioid cells are neoplastic is negated for the pathologist by their similarity to cells of accepted inflamma-

tory reactions and the dissimilarity of their pale nuclei and orderly growth to characteristic sarcoma cells. With increasing age of the lesion, fibrosis becomes more and more prominent, some nodes being almost entirely converted into fibrous tissue, with few of the earlier cells remaining—a condition common to many non-neoplastic lesions of lymphoid tissue, but rare in such extreme degree in untreated neoplasms. Even the cell degeneration and areas of necrosis appear to the pathologist's eye more like those of an infection such as tuberculosis or syphilis, than of neoplasm. The general histologic picture, to be sure, sometimes resembles superficially that of sarcoma or even a sclerosing type of carcinoma metastasis, but it also sometimes comes close to that of atypical tuberculosis.

The most important feature in the histologic picture that supports the neoplastic nature of Hodgkin's disease is the neoplastic development late in a certain number of cases of lymphoid tumors of the kind, called by Ewing, Hodgkin's sarcoma. However, as Ewing himself indicates, this picture is only found in a minority of cases. In fact, a critical review of the literature of such cases reduces acceptable cases to a very small number indeed. Such a picture, of course, can easily be reconciled with the infectious theory, by regarding it as a localized neoplastic transformation as a result of the chronic irritation, in the same sense that many other neoplasms are thought to originate. Thus we might say that the characteristic histologic picture of Hodgkin's disease could only be harmonized with the primary neoplasm theory, if one assumed that it was an inflammatory response, of a type not known in connection with any other neoplasms, to an existing neoplasm whose presence in the tissue cannot be demonstrated.

Metastasis. The spread of the process to distant parts, metastasis if you will, is no more indicative of tumor metastasis than of the unknown and hypothetical infectious agent initiating the process in several parts, or transmitting it by blood or lymph. Tuberculosis and various other infections can metastasize or spread throughout the body as well as neoplasms. The tendency to invade, that some have invoked to support the tumor theory, is sometimes less marked than is the tuberculous process in lymph nodes; certainly in Hodgkin's lesions morbid cells are not found in the capsule to the extent that they are in malignancy, and mitoses (except in the Hodgkin sarcoma form) are infrequent.

Fatal Outcome. Exponents of the malignancy theory invoke the invariably fatal outcome as an argument, but we have enough devastating infections, and some that work slowly, to let us accept with equanimity that another, especially when no potent treatment has been devised, might always be fatal. Leprosy was in the same stage a few years ago, while pernicious anemia, due to constitutional defect, was uniformly fatal until Minot's liver treatment was discovered.

Megakaryoblastoma. The latest exponent of a primary neoplastic origin of Hodgkin's disease is Medlar,[13] who suggests that it is a "megakaryoblastoma," arising from the megakaryocyte of the bone marrow. This was suggested by his observation in experimental tuberculosis (avian and bovine), both of numerous cells resembling the giant cells of Hodgkin's disease, which were taken to be megakaryocytes, and also of a hyperplasia of megakaryocytes in the bone marrow with a wandering-out into the tissues. In a further study of 22 human autopsies and about 100 surgical specimens (but including only 6 bone marrow instances), he found "hyperplasia of the marrow with a marked increase of immature cells which probably are the progenitors of megakaryocytes," with similar picture elsewhere in the body. Adopting the unitarian theory of hematopoiesis, the author suggests that Hodgkin's disease thus becomes closely related to the myeloid leukemias and the erythroblastic dyscrasias. A novel addition to the suggested etiology and nomenclature of Hodgkin's disease (Wallhauser lists 52 proposed names!), and apparently offered chiefly in a provocative way, this hypothesis does not excite one's enthusiasm. Aside from the general limitations on making difficult classifications solely on the basis of morphology, in this case a considerable further assumption is required, namely, that the immature cells in the bone marrow are progenitors of megakaryocytes. Nor do the illustrations furnish impressive support: Granted that the lesions are those of Hodgkin's disease—and I* believe that the bone marrow is more often involved in this disease than has hitherto been appreciated—and granted, of course, that the characteristic giant cell may be found in other tissues, sometimes even in mitosis, both items that are generally acceptable, this by no means indicates that a neoplastic megakaryocyte is necessarily responsible for the lesion. In fact, the very observations that led to elaboration of the theory, namely, the occurrence of similar cells in experimental tuberculosis, are evidence in support of an infectious rather than a neoplastic explanation for the picture found. The prevalent opinion that both endothelioid and giant cells are derived from the reticuloendothelial system has both *a priori* and evidential support.[14] Medlar also suggests that the prominent late fibrosis may be due to organization of excessive fibrin, the formation of which is connected with an increased number of platelets. The assumptions required to support such a view are too numerous to demand more than its notice.

No Demonstrated Etiologic Agent. An important argument that is raised against the infectious theory of Hodgkin's disease is the failure to find an accepted microörganismal cause. It must at once be admitted that the long list of diphtheroid bacteria, spirochetes, amebæ and (most recently) monilia and so on have not been acceptably substantiated.

* Am. J. Med. Sci., **182**, 764, 1931.

The most persistent of these claimants is some atypical form of the tubercle bacillus, both because of the well-known frequent association of the two diseases in question (Ewing's apt dictum that tuberculosis follows Hodgkin's disease like a shadow), but also because of suggestive positive evidence that has more than once been produced. Sternberg's frequent finding of tubercle bacilli in Hodgkin-like lesions led him to accept them as the active cause either of the disease itself or at least of a similar subvariety of pseudoleukemia. The latest contribution to this aspect, l'Esperance's[15] recovery of avian tubercle bacilli from Hodgkin's material and experimental production of Hodgkin-like lesions, is too recent to have reached final appraisal. Against her findings must be placed the failure of others to get similar results (but how often has this not been the experience of medical discoveries?) or to benefit patients with serum from inoculated fowls.[16] The vastly preponderating opinion of a whole generation (based mostly on failure to find acid-fast organisms or tuberculous lesions in Hodgkin's material) has been that there is no, or at most a secondary, relation of tuberculosis to Hodgkin's disease.

The most recent development in this field of etiology is the demonstration that ultramicroscopic material (Seitz filter) from Hodgkin's lesions, especially when rendered more potent by refrigerated maceration, can produce characteristic lesions when injected into rabbits and guinea pigs.[17] If the opinion is substantiated that this procedure has diagnostic value, it will not only be a great relief to have a biologic as well as a morphologic attack on biopsy material, but it also should advance our understanding of the disease and perhaps place it definitely in the group of virus diseases. With the known prevalence of latent virus diseases in laboratory animals, however, and their activation by non-specific agents, attribution to this virus of a causative rôle in Hodgkin's disease must be made with utmost caution. Although Fox's[18] small material has thus far been confirmatory, Rhoads and Stewart,[18] in New York, have not been able to reproduce Gordon's result.

Twort's[19] uniformly negative attempts to uncover an infectious agent led him to the pessimistic view, that "one might be dealing with a new growth," but fortunately such councils of despair rarely gain much support.

Immunity. Warthin[20] includes among the arguments for neoplasm that no evidence of immunity has been produced. But in the absence of a known specific cause, this objection hardly assumes serious proportions.

A Disease Between Infection and Neoplasm. The suggestion has been made that Hodgkin's disease is unique in being intermediary between infection and neoplasm. Except for the possible occasional sarcomatous transformation of the granuloma (*i. e.*, sarcoma not an integral part of the disease), this idea is both difficult to accept

and without progress value. Concepts of infection and of neoplasm and of transformation from infection to neoplasm are definite and useful, but a hybrid essentially between the two should not be admitted into the present etiologic scheme of disease.

Miscellaneous Evidence. A number of lines of evidence must be regarded as favoring neither infection nor neoplasm. Age, sex, seasonal incidence, geographic distribution, occurrence of the disease in several members of the same family, simultaneous occurrence in twins, and in mother and new-born child,[21] fever, anemia, reaction to irradiation, general signs and symptoms, duration and similar phenomena may with almost equal justification be invoked to support either the infectious or neoplastic hypothesis. The relapsing type of fever, eosinophilia and impossibility of transmission to animals have led Barron[22] to support the parasitic nature of the disease; but no parasite has been incriminated.

Thus, while it is apparent that the nature of Hodgkin's disease remains obscure, the preponderance of evidence favors the infectious theory, with some promising support for its inclusion among the virus diseases. It must be conceded, too, that the stimulus to further progress is greater if it is not included among the malignant neoplasms, at least until compelling evidence is forthcoming. Certainly the growing tendency in this country to relegate it to the already complex and ill-defined group of lymphoblastomata seems ill-advised, both as confusing, against the evidence and inhibiting progress. In the present state of our knowledge of the subject, the term "lymphogranuloma" is also inadvisable. The non-committal designation, "Hodgkin's disease," even though largely based on a picture unknown to the original describer, is to be recommended until a definite etiology has been established. It is a source of satisfaction, then, that the Lymphatic Tumor Registry has seen fit to preserve the independent position of Hodgkin's disease.

Summary. 1. The results of 33 cases of fatal Hodgkin's disease are briefly analyzed.

2. Evidence for the infectious or neoplastic nature of Hodgkin's disease is presented and discussed.

3. Use of the term Hodgkin's disease (rather than lymphogranuloma or lymphoblastoma) and restriction of its use solely on a pathologic (not a clinical) basis is demanded.

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THE DIFFERENTIAL DIAGNOSIS OF AGRANULOCYTIC ANGINA FROM ACUTE LEUKEMIA.

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For reasons that are not clear, the syndrome commonly called agranulocytic angina is now a relatively common one throughout the country. A few years ago the diagnosis was virtually never made, even in the large general hospitals. In the last few years scores of cases have been reported from all parts of the country. The reason for this apparent increase is not clear—it may partly be attributed to more complete and more careful hematologic studies and to better diagnosis; but we may be reasonably certain that the disease has actually increased very considerably. Its etiology and even its pathology are obscure. The condition carries with it a grave prognosis, even with the best of therapy. At the same time a considerable number of these cases recover either spontaneously or following the administration of some more or less specific drug and remain well over a sufficiently long period of time to be regarded as true cures. The condition, however, is easily confused with a far more serious disease—acute leukemia, which is generally conceded to be invariably fatal in a comparatively short period. These facts show the importance of careful differential

diagnoses. From my experience with these two diseases I have drawn certain conclusions which I would like to present briefly.

Let us consider 2 patients. The first is a man, aged 40. His previous health has been good, in fact he has been unusually strong. Three weeks before admission to the hospital he had a sharp chill, an increase of temperature and severe general malaise. Recovery was rapid and complete. Two weeks later a similar episode ensued. Again within 24 hours he seemed as well as ever. Two days before admission to the hospital he began to have malaise, sore throat, chills, generalized abdominal pain and a severe ache in the lower rectum. Prostration was marked. On examination he was found to be mildly delirious. The gums were swollen and ulcerated but not bleeding. The throat was red and parched looking. The temperature was 103° F. There were enlarged and tender lymph nodes in each side of his neck. The heart and lungs showed no abnormalities. The spleen descended two fingers below the ribs on inspiration. The liver was not palpable. In the rectum could be felt a soft, tender mass which did not bleed on palpation. His red count was 4,000,000 per c.mm., the white count 1200 per c.mm. and the platelets slightly increased. The differential count disclosed complete absence of neutrophils, over 90% of the white cells being mature lymphocytes. There were 2% stem cells and the remainder were young monocytes. The red cells showed no abnormalities.

The second case presented a somewhat similar picture. The patient was a man, aged 45. His past history was irrelevant. A week before admission he began to have profuse bleeding from his gums. Fever and sweating was noted from the onset. Malaise was extreme and the patient became rapidly weaker. Three days before admission several large ecchymoses appeared on the outer aspect of his thigh. There had been no preceding trauma. The day before entry he complained of pain in his rectum and passed a small quantity of bright blood. On admission, the physical examination showed him to be extremely pale and sweating profusely. The mucous membranes were pale and slightly cyanotic. The gums were swollen and bleeding profusely. There was some bleeding from his nose. There were palpable and tender lymph nodes in both sides of his neck. The heart and lungs were normal. The spleen was enlarged to the level of the umbilicus. Three large ecchymoses were present on the outer aspect of his right leg. Rectal examination revealed an exquisitely tender, soft, bleeding mass just inside the sphincter. The temperature was 100° F. and the pulse 90. Subsequent examination of the blood showed the white count to be 1000 per c.mm., red count 2,100,000 per c.mm. The platelets were completely absent. The differential count showed 100% stem cells. The red cells were achromic and a rare normoblast was seen.

The first case to my mind is typical of agranulocytic angina; the second a classic example of acute leukemia. There could, I believe, have been no reasonable doubt as to the diagnosis, and the ultimate outcome of the 2 cases proved the correctness of the original diagnosis. The first man is alive and well now, 3 years later; the second man died within a few months, and the bone marrow showed a picture entirely consistent with the diagnosis of acute leukemia.

The differential diagnosis between the two conditions rests largely on the blood picture and to a far less extent, in my opinion, on the signs and symptoms. In acute leukemia there is usually a great reduction of platelets, very frequently they are completely absent. This is not the case with agranulocytic angina, for in this disease the platelets are usually normal, often increased and very rarely diminished. In acute leukemia, anemia is usually marked and progressive and is of the macrocytic type. Anemia in agranulocytic angina is rarely, if ever, of any moment and when present is usually to be attributed to associated but unrelated causes and is of the microcytic type. In acute leukemia, especially in adults, the blood smear shows a considerable number of very immature cells, often virtually all the white blood cells are stem cells and it is only in the most atypical cases that young forms are few in number. A few stem cells may be found in the blood of patients suffering from agranulocytic angina; any very considerable number, however, indicates the probability of leukemia, and the more there are the greater the probability. A level is reached, perhaps 20%, which if more than temporary almost certainly means leukemia. During convalescence from agranulocytic angina there may be, and in fact usually is, a temporary outpouring of myelocytes, but this stage is soon passed and clinical improvement is evident coincidentally.

Agranulocytic angina is very rare in childhood. I have seen no case under 12 years of age and very few under 20. Acute leukemia is not uncommon in childhood, occurs most frequently in early adult life and is rare in old age. Agranulocytic angina is seen in a fair percentage of the cases in the aged.

Leukemic patients with temperatures of 102° to 104° F. may seem comparatively well. This is rarely the case with agranulocytic angina. In this latter disease such temperatures are almost invariably accompanied by marked prostration and toxicity. In agranulocytic angina the fever is either steady or more commonly fluctuates within certain rather definite limits. In acute leukemia the temperature curve is often an extremely variable one.

It should be emphasized that the total white count is of no vital importance in the diagnosis of leukemia. Leukemia is still leukemia whether the white count be 50 or 50,000 per c.mm. The character of the white cells and the pathologic changes in the bone

marrow determine the diagnosis. In the last analysis sternal bone marrow puncture may have to be resorted to as a diagnostic aid.

Our thesis so far seems simple and yet I am convinced that it is not. The first case to which I referred recovered and after a somewhat stormy convalescence has remained perfectly well for over 3 years, but so also did our second case recover temporarily in a manner not at all dissimilar from that of the first and with hematologic changes which were to a certain extent parallel. After 5 days, during which time he had been treated with pentnucleotid, there was a sudden drop in temperature and gradually, over a period of weeks, his blood returned to normal in every respect. The lymph nodes disappeared. The spleen and liver receded, the gums cleared and the patient returned to his usual work, with neither clinical nor hematologic signs of leukemia. He remained perfectly well for over 5 months, but then was suddenly seized with excruciating headache. A week before this episode his blood had been entirely normal. On admission, however, the white count was found to be 20,000 per c.mm., with 80% stem cells, and he was dead in 10 days. The bone marrow showed the characteristic picture of acute leukemia.

Acute leukemia is, of course, subject to temporary remissions, but they are rare and usually of very short duration and almost invariably either the clinical or the hematologic picture shows unmistakable signs of the continued presence of the disease. In the case under consideration, such was not the case. It must, therefore, remain an open question as to the exact nature of his first attack.

The more I see of cases of extreme leukopenia the more certain I become that the differential diagnosis between the various pathologic entities which underlie this syndrome may be well nigh impossible.

A woman, aged 60, whose past health had been good, was taken with severe right lower quadrant pain, chills and high fever. Her white count was found to be 1000 per c.mm., with 100% normal lymphocytes. The platelets and red count were normal. In 2 days she was dead and a retrocecal abscess was found at autopsy. To my mind the diagnosis lay between primary agranulocytic angina with secondary sepsis and primary sepsis with consequent leukopenia. An examination of her bone marrow revealed the fact that it was studded with miliary tubercles and the active myeloid elements had completely disappeared.

A man, aged 50, had had repeated attacks of extreme leukopenia with intervening intervals of perfect health. In all respects, so far as I am able to judge, the case was typical of the relapsing type of agranulocytic angina. However, gradually anemia developed, hemorrhages appeared, the intermittent extreme leukopenia became

constant and death ensued. The bone marrow again revealed miliary tuberculosis with aleukogenesis.

A man, aged 68, was admitted to the hospital with a classic picture of chronic myelogenous leukemia. The white count was 175,000 per c.mm. The spleen descended to the umbilicus. The liver was grossly enlarged. The patient received moderate Roentgen ray therapy without apparent benefit. Two months later the spleen had disappeared, the white count was 1000 per c.mm., the differential showed the vast majority of the cells to be normal lymphocytes. The platelets were normal. Had the patient been seen for the first time at this stage of his disease, he might well have been considered to have agranulocytic angina. He died shortly afterward, and at autopsy the bone marrow showed virtually complete absence of myeloid cells and great activity on the part of early red cells. The liver and spleen showed no gross or microscopic changes.

We must, I believe, recognize that the most classic leukemia can become not only aleukemic but also aplastic. We all recognize that similar bone-marrow changes may be reflected by varied blood pictures. It must also be remembered that very similar blood pictures may be associated with the most varied pathologic changes in the bone marrow and other organs.

In any consideration of the etiology, therapy or diagnosis of any condition it is wise, I believe, first to ask whether the condition under consideration be a distinct entity, recognizable as such by biopsy or postmortem examination. If it is not, I believe our efforts should be aimed toward the clarification of this angle of the subject. We have recently reviewed very carefully the bone marrow on some 20 cases which showed extreme leukopenia without significant involvement of the red cells. The pathologic pictures found varied so much that, frankly, we were unable to give many of them any specific diagnosis. Some we believe to be true and classic agranulocytic angina, others with clinical pictures, not very dissimilar, have shown postmortem many of the earmarks of leukemia. Still others reveal what, for lack of a better term, we refer to as aleukogenesis, no representatives of the myeloid series being present. No doubt the criteria set forth in the beginning of this paper will suffice in many instances to draw a distinction between agranulocytic angina and acute leukemia; but it is my belief that until this former disease, or rather syndrome, is placed upon a more sure pathologic foundation it will be difficult, if not impossible, to distinguish the less fatal types of leukopenia from the probably always fatal acute leukemia.

FIVE-YEAR SURVIVAL IN HODGKIN'S DISEASE.

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As Hodgkin's disease is uniformly regarded as incurable, no one attempts to speak of 5-year cures, as in cancer. As was emphasized by Stone, of this hospital, 10 years ago, the best results in treating Hodgkin's disease are obtained if one accepts its incurability as a fact and proceeds accordingly with therapeutic measures designed to secure the best palliation for the longest possible time. Such an attitude is not inconsistent, however, with the use, at times, of rather heavy irradiation. Yet it does restrain one from the needless overburdening of the patient with such massive doses as are employed to good purpose, for instance, in the Coutard technique of treatment of hypopharyngeal cancer.

The average length of survival of patients with Hodgkin's disease from the time the symptoms appear is 3 years or less. It is well known that some cases run a much more rapid course, while a few stand out as having run a much longer course. Stone showed that of 164 patients there was complete restoration of health after treatment, either with or without complete disappearance of objective evidence of disease in 32 per cent. In these cases the duration of life subsequent to treatment averaged 35 months, as compared with an average of only 16 months for the whole group.

Among the more important reports concerning length of survival in Hodgkin's disease after irradiation are the following:

Burnam reported 28% of 147 cases showing a survival of 5 years or more following Roentgen therapy, with 14 surviving 8 years or more. These results are so exceptionally good that the question arises as to what proportion of cases in this series did not have the diagnosis confirmed by biopsy. Schreiner and Mattick, in 1924, reported 46 cases, of which 31 had been treated by high voltage Roentgen rays or radium pack. Their average survival was 2 years and 7 months. (It is not clear whether this figure represents survival following irradiation or recognized onset.)

Voorhoeve, in 1926, reported 19 cases. Of 11 which had been treated according to plan, 7 were dead, with an average survival of $2\frac{1}{2}$ years following irradiation, and 4 were living with an average survival of 3 years.

Gilbert and Babaiantz, in 1931, reported that of 25 cases treated since 1922, there were 15, all verified by biopsy, that had received treatment according to plan. These had the remarkable average survival following Roentgen therapy of 4 years and 9 months.

Five patients died after an average survival of $2\frac{1}{4}$ years. Four died on an average of $4\frac{1}{2}$ years following Roentgen therapy. It is noteworthy that 6 of the 15 patients were living an average of over $7\frac{1}{4}$ years. Gilbert and Sluys take pains to point out, however, that since 1928 they have received 27 new cases and that they can see already that in this group they are not going to obtain as long an average survival as in the cases reported. They, therefore, advise great caution in judging individual results.

McAlpin and Golden, in 1933, reported 42 cases with positive biopsies. Five patients were still living at the time of their report, 2 for over 10 years. Of the 32 patients who had been followed throughout their course, 6 had survived over five years. In the deceased patients, however, the average duration of the disease was only 2 years and 8 months.

Analysis of Memorial Hospital Figures. A recent survey of the case records of this hospital gives the following figures. From 1918 to June 1, 1929, 125 cases of Hodgkin's disease verified by biopsy were treated. Because of the fact that for several years we pursued the fad of treating cases of supposed lymphosarcoma and Hodgkin's disease largely without benefit of biopsy, we have in our records a considerable number of additional cases which, because of their clinical course, we have good reason to believe were Hodgkin's disease; 185 cases, in fact. A third group of 53 more doubtful cases is not included. This makes a total of 310 cases either proven by biopsy or believed to be proven by clinical course, treated between 1918 and June 1, 1929.

Of these 310 cases, 32 (10.3%) showed a survival following irradiation of 5 years or over. Of the proven cases, numbering 125, 15 (12%) showed a survival of over 5 years.

Living are 16 patients over 5 years since they came, in 9 of these the diagnosis being proven by biopsy. These 9 living patients have survived an average of 7.4 years since treatment and have an average total duration of life since onset of symptoms of 9.5 years.

Our service in the treatment of Hodgkin's disease has increased considerably in recent years. We now have in the current file, records of 77 cases, proven by biopsy, and 17 cases, without biopsy, but almost certainly Hodgkin's disease. A number of doubtful cases is excluded.

As an attempt to find reasons for the marked extremes of duration, of course we have made for comparative purposes a brief analysis of a group in which there was a total survival of 1 year or less following onset of symptoms and a survival of 6 months or less following irradiation. In this group were 22 cases, of which 9 were proven by biopsy and 13 were presumably Hodgkin's disease.

As to age of patients, we find that the 5-year survivors averaged 34 years of age and varied between extremes of 6.5 and 67 years, while those surviving 6 months or less averaged 44.3 years and

varied from 7.5 to 67 years. Thus we find that there is practically no difference between these two groups with respect to age limits, and we also find the rather surprising fact that the patients with the shorter courses were, on the average, 10 years older.

The male-female ratio was 11 to 10 in the 5-year group; 14 to 8 in the 6-month group.

As to average duration of the disease before treatment, we find in the group of 5-year survivors that the symptoms had existed previously for from 1.5 months to 8 years, the average being 1.4 years; while in the 6-month cases, symptoms had been present previously for from 1.5 months to nearly 1 year, the average being 4.4 months.

What reasons can we find in our survey of these two contrasting groups of cases for the great difference in length of course? The simplest statement, but one which does not explain the difference, is that the disease was more virulent or malignant in the one group. An analysis of the presenting complaints in the two groups indicates that in the cases of short survival there was evidence of generalization in 16 of the 22, while in the cases with long survival uncomplicated lymphadenopathy with few or no general symptoms was the rule. We have seen that, contrary to the usual impression, the cases with the longer survival were not in the older age groups, but in the younger, averaging 34 years as against 44.3 years.

Examination allows us to say with safety that variations in histology of nodes as removed at biopsy do not account for the different duration of course. Many of the cases pursuing the longer courses have shown highly cellular types of Hodgkin's disease, approaching sarcoma.

As to location of disease we have the distinct impression that localization in one area, preferably the upper cervical region, combined with early thorough treatment, perhaps with early surgical removal followed promptly by thorough irradiation, offers the most favorable prognosis.

A nearly normal blood count seems to be favorable, while leukocytosis with or without polynucleosis, or leukopenia, are unfavorable.

Fever and marked pruritus, and pronounced splenomegaly seem to be unfavorable prognostic signs.

A tendency to gain greatly in weight soon after irradiation seems to be a good indication.

Yet 1 of our patients now living, 8 years since treatment was begun, had advanced pulmonary tuberculosis with cavity formation and positive sputum when admitted.

As to treatment, the long-surviving cases on the whole seem to have fared with only a moderate amount of irradiation; but this statement should be qualified, I think, by stating that, as a rule, in the cases with long survival the early lesions were treated fairly vigorously and persistently.

I should like to add a statement of impression concerning our present technique which consists mainly of divided doses of high voltage Roentgen therapy, as contrasted with the technique of 5 and 10 years ago, when for the most part single massive doses of low voltage Roentgen rays were used. Our regressions now seem better with less immediate discomfort, but are we not seeing more marked leukopenia and more cases of later debility and leukopenia than in former years? I wonder whether some cases might not do better with the older technique.

Summary. Of 310 cases of Hodgkin's disease, 125 proved by biopsy, 10.3% showed a survival following irradiation of 5 years or over—of the proven cases, 16.8%.

Five-year survivors averaged 10 years younger (34 years of age) than a group that had survived 6 months or less, though extremes of age were the same in the two groups.

The difference in survival of the two groups is apparently due to differences in virulence of the disease. This, however, showed no correlation with the histologic appearance of nodes removed at biopsy. Favorable features were localization in one area, combined with early thorough treatment, absence of leukocytosis or leukopenia, gain in weight after irradiation. Fever, marked pruritus and splenomegaly were apparently unfavorable signs.

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IRRADIATION IN LYMPHOSARCOMA, HODGKIN'S DISEASE AND LEUKEMIA.

(A STATISTICAL ANALYSIS.)

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NEARLY 15 years have now elapsed since the introduction of deep Roentgen ray therapy, which has produced such pronounced changes in our concepts regarding the value of irradiation in general and of the curative results in particular. It, therefore, appears proper that, at a meeting to commemorate the fiftieth anniversary of one of the leading institutes for the treatment of cancer and allied diseases, we pass in statistical review all that has been accomplished in this domain, therefrom certain conclusions concerning standardization of rational therapeutic procedure may

be derived. Especially is this true of some affections of the lymphatic and hematopoietic systems, such as lymphosarcoma, Hodgkin's disease and leukemia, where radiation therapy, because of the extremely high radiosensitivity of the elements comprising those lesions, played a great rôle from its very incipiency.

This review of reports from the literature and of personal observations is concerned with the status which radiation therapy now occupies in the treatment of these conditions. There will be little, if any, new contribution, for the subject is already well covered in all its phases by a wealth of material; but the numerical tabulation of results from distant parts of the world may help to endorse certain more or less universally preferred methods and to harmonize various views concerning the optimum therapeutic effect which may be expected. To this aim, attention will be directed to the following main points: (1) Increase of expected duration of life in the average case; percentage of 5- and 10-year survival with eventual final cure in the individual cases; (2) method of treatment which appears more generally used leading to the optimum effect; and (3) prognostic evaluation during the course of the disease and treatment.

(*a*) *Lymphosarcoma.* The paucity of the statistical material concerning irradiation of lymphosarcoma is indeed surprising. This is chiefly due no doubt to the lack of knowledge as to what really constitutes lymphosarcoma and in the rather vague precision as to its classification. It seems that the majority of investigators still prefer to consider the condition as a small round cell sarcoma and thus to place it in the rather large group of general sarcoma, without further subdivision or classification. On the other hand, the very close resemblance which exists between this condition and other disorders affecting the lymphoid tissue, such as pseudoleukemia, aleukemia, Hodgkin's disease and even lymphatic leukemia, has induced not a few students of the problem to include them all under the general heading of lymphoblastoma or malignant lymphoma. To take one example of this latter group: Minot and Isaacs,[21] who on the basis of a rather large number of cases (477) arrived at some very definite conclusions concerning certain points which are of interest to us, state that the average life duration of lymphoblastoma is 2.76 years and that about 10% of both the irradiated and non-irradiated had the disease for 6 or more years. From this they think that radiation therapy, although of great value in producing symptomatic improvement, does not influence importantly the life duration of the group as a whole. Obviously it is very difficult, if not impossible, to obtain comparative data either by including lymphosarcoma in the general group of sarcoma or by placing it under the comprehensive heading of lymphoblastoma. Desjardins and Ford,[9] well realizing this difficulty, published, in 1923, a first series of 55 cases of lymphosarcoma to determine the life expectancy from the onset of symptoms to death, when no sys-

tematic treatment was given and, in 1926, a second series of 126 cases to ascertain the prolongation of life when radiation therapy was applied. The average duration of life was found to be in the first series $2\frac{1}{2}$ years and in the second $2\frac{1}{3}$ years, indicating that radium and Roentgen ray treatment does not seem to prolong life to a notable degree. The percentage of those who survived longer than 5 years was 10 in the first series and 6 in the second, the longest life duration being 25 years. These results agree well with those of Minot and Isaacs.

TABLE 1.—STATISTICAL ANALYSIS OF RESULTS IN LYMPHOSARCOMA

(The group of lymphoblastoma of Minot and Isaacs is included for purposes of comparison.)

Author.	Period.	Type of lesion.	Cases.	Irradiation technique.			Results.					
				Quality.	Dose.	Extent.	Untraced.	Alive.	Lived. 5 yrs.	Lived. 10 yrs.	Died.	Average survival since onset, yrs.
Minot and Isaacs,[21] 1926	1913–1925	All lymphoblastoma except lym. leukemia	477	No irradiation			..	76	60	16	163	2 45
	1901–1925			Various irradiation							238	2 88
Desjardins and Ford,[9] 1923	1915–1920	All lymphosarcoma	102	Without systematic treatment			26	9	6	..	67	2 45
Desjardins,[10] 1926	1920–1923	All lymphosarcoma	126	140 Kv. 200 Kv.	Large doses	Fairly general	32	25	7	2	69	2 33
Rosenthal, Harris and Kean,[28] 1931	1918–1931	Follic. lymphosarcoma	10	200 Kv.	Fract. 200 r.	All reg. involved	..	4	4	1	6	4 33
Evans and Leucutia,[11] 1934	1922–1930	All lymphosarcoma	31	200 Kv.	Large doses	Generalized	1	6	10*	4	24	3 33†

* Four died later.

† The average life duration since treatment was 2.1 years.

A tabulation of 31 cases of lymphosarcoma treated from 1922 to 1930 at Harper Hospital shows, however, that systematic irradiation leads to a distinct improvement in results. In our series, 30% lived 5 years or longer, 15% 10 years or longer (for some of the 5-year survivals the 10-year period is not up yet). For those who died, the average duration of life was $3\frac{1}{3}$ years after the onset of symptoms and 2 years and 1 month after the beginning of irradiation. Still better results were reported by Rosenthal, Harris and Kean[28] for 10 cases of follicular lymphoblastoma, a more benign variety than other types of lymphosarcoma. In their series, 4 patients are alive from 3 to 12 years, and in the 6 who died the average life duration from the onset of symptoms was $4\frac{1}{3}$ years.

Although the material gathered in this group is not very large, and certainly not as comprehensive as in the groups of Hodgkin's disease and leukemia, we may venture the following statement concerning the value of irradiation in lymphosarcoma:

1. Thorough radiation therapy increases the expectation of life in all forms of lymphosarcoma from 2½ to 3½ years and leads to cure in at least 10% to 15% of the cases. If a subdivision into reticulum cell sarcoma, lymphocytoma and follicular lymphoblastoma is made, the improvement in results shows an ascendancy in the order named. Adding to this the often-observed "spectacular" symptomatic improvement, the largest tumors melting away like snow within the period of a few days, radiation therapy must be considered as the method *par excellence* in the treatment of lymphosarcoma.

2. It is essential that irradiation be carried out with penetrating rays (200 kv., ½ to 1 mm. Cu or Zn as filter), large doses (90% to 100% SUD per field) and wide extension to as much as possible of the lymphatic system, the entire abdomen and the mediastinum being included in the series of exposures, regardless of whether the disease is localized or generalized. It is not unusual by this procedure to have 16 to 20 large portals covered with full or nearly full erythema doses within a period of 2 or 3 weeks, the total amount of radiation absorbed by the body being indeed a considerable one. A severe depletion of the blood with all its sequelæ follows shortly after the completion of the series and, therefore, a very careful management of the patient with administration of blood stimulants and roborants is necessary for several months. The irradiation is repeated in 8 to 10 weeks over the areas of the manifest lesions, which by this time have all disappeared, with a dose of about 70% SUD; and eventually for a third series in another 10 to 12 weeks with a dose of 50% SUD. Since lymphosarcoma, by reason of the lymphatic extension, remains localized to the lymphatic system and a few abdominal organs, such as the intestinal mucosa, serous membranes, spleen and liver, for a longer time, the above procedure leads in a certain percentage of cases, as shown in the statistical analysis, to a complete eradication of the disease. In such instances, no resumption of the irradiation appears necessary after the series is once completed, patients remaining free of recurrences for long periods or becoming cured. This, as we shall see later, is contrary to what occurs in Hodgkin's disease or leukemia. In case there is only temporary regression or the dissemination of the disease continues at a more or less rapid pace, irradiation acquires a purely palliative value and is directed accordingly.

3. The prognosis of lymphosarcoma is governed apart from the radiosensitivity gradation into the three forms (the reticulum cell sarcoma, lymphocytoma and follicular lymphoblastoma) by the extent of involvement at the time of the treatment and especially by the rapidity of growth of the tumor in the period preliminary to treatment. Lesions localized for a longer period to one single lymphatic region, as a rule, are more apt to result in final cure than widely disseminated rapidly growing processes, although in a few

instances we have experienced a complete disappearance of the lymphosarcoma with more than 10-year survival in very generalized forms. Progressive anemia, gradually developing cachexia, onset of fever, etc., usually render prognosis unfavorable.

(*b*) *Hodgkin's Disease.* In contradistinction to lymphosarcoma, Hodgkin's disease formed a favored topic for statistical study to a rather impressive number of investigators, so that in Table 2 we were able to collect the final results of 14 leading institutions from different parts of the world, based on some 805 cases. As is noted, there is a very close agreement between the various sources, the rationale of the following general conclusions being quite apparent:

1. Radiation therapy, if carried out systematically, in addition to the fact that it leads to great symptomatic improvement, increases the duration of life in the average case of Hodgkin's disease from 2 to about $3\frac{1}{2}$ years, produces a 5-year survival in 15% to 33% of cases, a 10-year survival in 8% of cases and finally leads in certain instances to a symptom-free period long enough beyond the 10-year limit that it may be considered a cure. If the acute cases as well as those which, because of the very far advanced stage, could not be properly treated, are eliminated or set in a group apart, as practised by Voorhoeve,[31] Gilbert, Babaiantz and Sluys,[14] Hummel[17] and others, the good effect of the irradiation becomes still more apparent. In view of the fact that no other method can equal these results at the present time, radiation therapy must be considered as the treatment of choice.

2. As a general rule, Roentgen ray therapy with penetrating rays (160 to 200 kv., $\frac{1}{2}$ to 1 mm. Cu or Zn as filter) is preferred, although some favorable results are reported also with radium packs which, however, must possess a rather marked intensity. The so-called medium Roentgen rays (120 to 130 kv. with light Al filter) are now practically discarded or reserved for the occasional irradiation of the spleen. The dosage is guided by the general condition of the patient and the severity of the lesion. If the condition is good and the lesion localized, larger doses up to a full erythema dose may be attempted, but if the condition of the patient indicates systemic invasion (fever, pruritus, modification of the blood formula, cachexia, etc.) and the manifest lesions are fairly generalized, the fractionated protracted method will lead to best results. Daily seances of 10% to 30% SUD are given spread over a period of several weeks until all disease foci are covered, a total dose of 50% to 90% SUD being administered per focus. The massive irradiation with large single doses including all lymphatic areas, whether diseased or not, as heralded in the early period of deep Roentgen ray therapy and as successfully practised for lymphosarcoma, has brought only disappointment in the treatment of Hodgkin's disease. It has, therefore, gradually given way in every place where it was used to the more moderate procedures, as

TABLE 2.—ANALYSIS OF RESULTS IN HODGKIN'S DISEASE.

TABLE 2.—ANALYSIS OF RESULTS IN HODGKIN'S DISEASE.

Author.	Period.	Cases.	Irradiation technique.			Results.								
						Untr.	Alive.	Aver. life duration, yrs.		Lived.		Died.	Aver. survival, yrs.	
			Quality.	Dose.	Extent.			Since trtm.	Since onset.	5 yrs.	10 yrs.		Since trtm.	Since onset.
Desjardins and Ford,[9] 1923	1915–1920	135	Without systematic treatment			43	10	..	..	7	..	82	..	2.55
Desjardins,[10] 1926	1920–1923	57	140 Kv. 200 Kv.	Large doses	Generalized	10	11	..	..	6	2	36	..	3.15
Chaoul and Lange,[8] 1923	–1923	12	1 mm. Cu	70% SUD; foc. fract. of 10%	Only manifest lesions	..	1	..	..	1	..	..	2.5	3.0
Schreiner and Mattick,[29] 1924	–1924	46	140 Kv., ½ Cu 200 Kv., ½ Cu Radium pack	70% SUD	...	..	..	..	..	..	..	..	..	2.55
Voorhoeve,[31] 1925	1915–1925	I:11 II: 8	160 Kv., ½ Zn or 200 Kv., ½ Zn	70% SUD; foc. fract.	Manifest lesions	..	4 2	3.0 0.25	4.4 1.25	..	..	7 6	2.6 1.7	3.8 2.3
Brugman,[4] 1926	1913–1925	20	...	50% SUD; foc. fract.	Manifest lesions	8	1	3.5	..	..	..	11	2.5	
Burnam,[5] 1926	1913–1925	173	Radium pack	25% SUD; foc. fract.	Manifest lesions	.. 13	9 28	.. 5.15	4.25 6.25	9	4	110	2.9	4.25
Dautwitz,[3] 1927	–1926	56	Radium pack	Small doses	Manifest lesions	6	6	4.6	..	..	1	44	..	3.0
Billich,[2] 1930	1920–1930	31	180 Kv., ½ Zn	Sm. fract. 20% SUD foc.	Manifest lesions	..	..	..	..	..	..	..	..	2–3
O'Brien,[28] 1931	1919–1928	19	140 Kv., ¼ Cu	Small fract.	Manifest lesions	..	..	..	..	..	..	19	..	3.9
Hummel,[1] 1932	1920–1928	I:52 II: 4	....	70–100% SUD; later fract.	Manifest lesions	..	10	5.3	6.2	2	1	42 4	1.9 0.2	3.4 1.3
Goia,[12] 1932	1920–1932	63	180 Kv., ½ Zn or Cu	Fract. 150–400r p. field	Manifest lesions	..	17	4.25	5.33	6	1	46	2.25	3.2
McAlpin and Golden,[19] 1933	–1932	42	Med. volt., 3 Al; 200 Kv., ½ Cu	½–¾ SUD ½–¾ SUD	Manifest lesions	5	5	..	5.8	..	2	32	..	2.66
Gilbert, Babaiantz, Sluys,[14] 1933	1922–1928	I:15 II:10	Semi-penetr. 200 Kv., 1 Cu	Fract. 170r For. 400r	General; later only manifest lesions	..	6	7.25	..	5	1	9 10	3.5 1.6	
Evans and Leucutia,[11] 1934	1922–1930	46	200 Kv., 1 Cu	70–90% SUD; later fract.	Manifest lesions	..	10	..	..	10*	3	36	2.1	3.1

* Five died later.

The subdivision of Voorhoeve, Hummel and Gilbert, Babaiantz and Sluys indicates: I, Those cases which received rational treatment and, II, those in which treatment had to remain incomplete because of subsequent complications.

indicated above, only the actually diseased areas being exposed. Following the completion of the first series, the patient is kept under strict surveillance, and as soon as there is evidence of a new focus or of a recurrence, the treatment is resumed. It is generally found that irradiation often must extend over a period of years, many of the 5- and even 10-year survivals being kept alive only by this continuous resumption of the irradiation. If in the advanced stages of the disease, the extension manifests itself only by general symptoms (fever, pruritus, anemia, cachexia, etc.), irradiation of the entire trunk with large fields or teleroentgen therapy will bring about further temporary improvement and relief of symptoms. Here the administration of adjuvants (arsenic, blood stimulants), opotherapy, climacteric therapy, etc., will likewise prove of benefit.

3. If one attempts a prognostic evaluation of a certain case of Hodgkin's disease during the course of the radiation therapy, it may be said that the prognosis is more favorable in the localized form, especially if the lesion remained confined for a longer period to one single group of glands or to one organ. In the generalized form it is more favorable in those cases which run no fever and have a normal blood formula and, finally, in all instances in which there is a prompt regression of the tumefactions following irradiation with long periods of remission. According to Goia,[15] who made a very detailed study of this subject, the prognosis is unfavorable in case of combination with active tuberculosis, involvement of the retroperitoneal glands, elevated and continuous temperature, hyperleukocytosis, exudative pleural or peritoneal effusion, hyperneutrophilia, neutropenia associated with leukocytosis, hypereosinophilia and a rapid recurrence of the tumefactions following radiation therapy.

(*c*) *Leukemia.* In estimating the precise value of irradiation in leukemia, it appears advisable to separate the acute from the chronic form. Especially is this true of the lymphatic type, where the ratio of the acute to the chronic form may be as high as 1 to 1 or even higher. Since radiation therapy is without even as much as symptomatic effect in the acute cases, the disease continuing its progression toward the fatal end at a rapid pace, their inclusion in the general statistics of leukemia serves only to confuse the issue in the chronic form. To take one example, Cooke,[7] from a study of 50 cases of acute lymphatic leukemia, found that more than one-half lived 3 months or less from the onset; one-third, 3 to 6 months; and only one-eighth from 6 to 9 months, none having survived the 9-month period. This is also the experience at this hospital following the systemic irradiation of 21 cases of acute lymphatic leukemia. On the other hand, Minot and Isaacs,[22] from a study of 30 cases of chronic lymphatic leukemia, without irradiation, estimated the average duration of life from the onset of the disease

in this form as being $3\frac{1}{3}$ years. By combining the two varieties, without specifying their ratio of incidence, obviously one may obtain an average life duration which varies from 1 to 3 years. This point is emphasized in order to furnish an explanation for some of the apparent discrepancies in the statistics of those investigators who, as shown in Table 3, made no distinction between the

TABLE 3.—ANALYSIS OF RESULTS IN LYMPHATIC LEUKEMIA.

Author.	Period.	Type.	Cases.	Irradiation technique.			Results.					
							Untr.	Alive.	Lived.		Died.	Average survival, yrs., since onset.
				Quality.	Dose.	Extent.			5 yrs.	10 yrs.		
Minot and Isaacs,[22] 1924	–1924	Acute	I:42	No irradiation			..	..	..	..	42	0.3
			II:15	Var. irradiation			..	..	..	..	15	0.3
		Chronic	I:48	No irradiation			18	..	..	..	30	3.33
			II:50	Var. irradiation			..	..	..	..	50	3.53
Béclère and Béclère,[2] 1913	1904–1913	Both	12	Benoist 9°	Small	Spleen Lymph nodes	..	..	1	..	12	
Schreiner and Mattick,[30] 1924	–1924	Both	16	90 Kv., 4 Al 200 Kv., ½ Cu Radium pack	Fract.	Spleen Lymph nodes General	..	..	..	..	16	
Fricke,[13] 1928	1915–1928	....	55	Radium pack	...	...	..	..	1	..	..	2.75*
Nyström,[24] 1931	–1931	Both	33	160 Kv., ½ Cu	$\frac{1}{30}$ SUD twice wkly.	Chest, back, abdomen	..	..	..	..	..	1.2
McAlpin, Golden, Edsall,[20] 1931	1920–1930	....	23	135 Kv., 3 Al 200 Kv., ½ Cu	$\frac{2}{3}$ SUD wkly. $\frac{1}{3}$ SUD wkly.	Sprfel. lymph nodes; deep lymph nodes	2	5	1	..	16	1.5
Arendt and Gloor,[1] 1932	1921–1931	....	26	170 Kv., ½ Cu Zn	10–40% SUD 40% SUD; also AS	Spleen Lymph nodes	..	..	6	2	20	2.2
Finzi,[12] 1932	1920–1927	Both	16	140 Kv., 5 Al 180 Kv., ½ Cu	80% SUD 100r daily	Spleen Lymph nodes	..	..	1	..	..	1.5
Cooke,[7] 1933	1917–1932	Acute	50	Var. irradiation and transfusion			..	..	..	..	50	0.3–0.9
Evans, Leucutia,[11] 1934	1922–1930	Acute	21	140 Kv., 4 Al 200 Kv., 1 Cu	50% SUD 30% SUD	Spleen Lymph nodes	1	..	..	..	21	0.4*
		Chronic	13								12	4.33

* Fricke's cases had an average survival since treatment of 0.95 year; Evans and Leucutia's of 2.5 years.

two forms. The final impression is that irradiation not only does not lead to a prolongation of life, but produces a shortening of life as compared to the values of Minot and Isaacs.[22] There is still another point worthy of consideration: in the statistics of Minot and Isaacs,[22] 1.4 years was taken in the chronic forms of both the lymphatic and myelogenous leukemia as the average period which has elapsed between the onset of the disease and the establishment of the first diagnosis. Since it cannot be said that patients are referred for irradiation any sooner, it would be perfectly proper to add the same figure to the final values of those Roentgen thera-

peutists who calculated the average period of survival of their patients from the time of the institution of the radiation therapy. With these corrections, we then find a rather close agreement between the various statistics as indicated in Tables 3 and 4.

TABLE 4.—ANALYSIS OF RESULTS IN MYELOGENOUS LEUKEMIA.

Author.	Period.	Cases.	Irradiation technique.			Results.					
						Untr.	Alive.	Lived.		Died.	Average survival since onset, yrs.
			Quality.	Dose.	Extent.			5 yrs.	10 yrs.		
Minot, Buckman, Isaacs,[23] 1924	–1924	88	No irradiation			36	..	18	3		3.04
		78	Var. irradiation, chiefly radium								3.5
Béclère and Béclère,[2] 1913	1904–1913	93	Benoist 9°	4H fract.	Spleen	..	..	..	..	93	
Klewitz and Schuster,[18] 1922	1912–1922	26	...	...	Spleen	..	..	..	..	26	2.5
Schreiner and Mattick,[20] 1924	–1924	9	90 Kv., 4 Al 200 Kv., 1 Cu Radium pack	...	Spleen	..	..	..	..	9	2.25
Fricke,[13] 1928	1915–1928	102	Radium pack	...	...	..	..	..	..	..	3.0*
Rikl,[27] 1930	1920–1930	31	160 Kv., ½ Zn	50% SUD fract.	Spleen	..	..	..	..	31	1–4
Hoffmann and Craver,[16] 1931	1918–1930	75	Radium pack 150 Kv., 4 Al	Small	Spleen	..	..	..	4	71	3.36
McAlpin, Golden, Edsall,[20] 1931	1920–1930	24	200 Kv., ½ Cu	⅛ SUD wkly.	Spleen	1	5	..	..	18	3.0
Nyström,[24] 1931	–1931	54	160 Kv., ½ Cu	$\frac{1}{30}$ SUD, 3–5 wkly.	Spleen Long bones	..	..	..	..	..	2.9
Radojevic,[26] 1932	1927–1932	18	Med. volt., 5 Al Deep 1 Cu	40% SUD 10% SUD	Spleen	..	..	..	..	..	3.9
Finzi,[12] 1932	1920–1927	38	140 Kv., 5 Al 180 Kv., ½ Cu	50% SUD 100r	Spleen Long bones Chest	..	..	..	..	..	1.95
Arendt and Gloor,[1] 1932	1921–1931	39	170 Kv. ½ Cu, Zn	10–40% SUD Fract. AS	Spleen	..	..	..	..	..	4.1
Evans and Leucutia, 1934	1922–1930	18	140 Kv. 4 mm. Al	50% SUD fract.	Spleen, occ. long bones	..	..	..	..	18	3.3*

* Fricke's cases had an average survival since treatment of 1.5 years; Evans and Leucutia's of 2.1 years.

It may be said, from a study of these statistics, including 420 cases of lymphatic and 683 cases of myelogenous leukemia, that:

1. Radiation therapy increases the expectation of life in chronic lymphatic and myelogenous leukemia very little, perhaps with about ⅓ to ¼ of the usual duration without treatment. Several authors are of the opinion that the results are somewhat better in the myelogenous group than in the lymphatic group, but this is not at all apparent if a careful separation of the acute from the chronic cases is made in the lymphatic group. In exceptional

instances (about 1% of the total) patients had a symptom-free life for a rather long period, the longest case in the lymphatic group having survived for 16 years and in the myelogenous group for 16.5 years. Most of these cases, however, have shown an exceedingly chronic nature from the beginning and they did not come to treatment until in the later stages of the disease, when the survival already exceeded the average period of life expectation. Thus if, on the basis of the above statistics, it cannot be said that radiation therapy leads to a cure even in individual cases of leukemia, and if life is prolonged but little beyond the expected duration in the average case, the question arises whether irradiation has a *raison d'être* in the treatment of leukemias or whether one may be content to produce palliation by other non-radiologic methods. A brief observation of the radiation effect should give the correct answer. In nearly every instance, the severe cases not excepted, a prompt and definite response appears shortly after the first few seances of irradiation. The patients are rapidly relieved of their distressing symptoms, start to gain gradually in weight and strength and within a few months are able to resume their work. From this moment on, with the aid of periodic check-up examinations of the blood formula as a guide, the good control of the symptoms can be continued by small series of irradiation given from time to time. It is said that the patient's working efficiency is increased at least 60% throughout the entire course of the disease as a result of the radiation therapy. Whether or not one accepts this as a proven fact, there can be no doubt about the great comfort which is brought about in the great majority of the average cases, so that here, too, we may affirm unhesitatingly that radiation therapy forms the best method of treatment to be followed.

2. There is virtual chaos concerning the technique of irradiation recommended. However, in view of the facts that palliation is all that can be produced and that some effect may be expected from every radiation, no matter under what circumstances and over which part of the body administered, this is not of great importance. Indeed, we see good results claimed from the medium penetrating rays (120 to 130 kv.) with larger doses (50% to 70% SUD) as well as from the harder rays (200 kv.) with smaller fractionated doses (10% to 40% SUD) and from the radium packs; whether the irradiation is made over the spleen, lymphatic system (especially in lymphatic leukemia), long bones (especially in myelogenous leukemia), great vessels of the chest, bones of the thorax, kidneys, entire trunk or even the entire body in the form of teletherapy. From a study of the statistics, it appears safe and perhaps best to pursue the following course: (*a*) Lymphatic leukemia—the spleen is irradiated with either half erythema doses of medium penetrating or with smaller doses of harder Roentgen rays and the enlarged lymph nodes are treated simultaneously with the

harder rays by making use of the protracted fractionated method which is spaced so as to conform with the changes in the blood formula; (*b*) myelogenous leukemia—the spleen alone is treated by using half erythema doses of the medium penetrating or smaller doses of the harder rays. The series which usually extends over 2 or 3 months is repeated at shorter or longer intervals depending on the blood formula, and only if no further response is obtained from the exposure of this organ is irradiation extended to the long bones or to the entire body in the form of teleroentgen therapy.

3. The aim of the radiation therapy being to bring about a symptomatic relief and improvement in the general condition of the patient rather than the eradication of the leukemia as a disease, it is unnecessary, even harmful, to try to reduce the white cell count to normal or below normal. If the state of the patient is good and the white cell count is in the neighborhood of 10,000 to 30,000, the irradiation may be temporarily discontinued. Future treatment is then guided by the activity of the leukemia, controlled by periodic blood examinations and a strict surveillance of the general condition of the patient. As soon as there is recurrence of the splenic enlargement or of the tumefaction of the lymph nodes, an increase in the relative or total white cell count of the blood, excessive rise in the number of immature cells and, finally, deterioration in the physical state of the patient, the irradiation is resumed. The anemia, which, as a rule, complicates the later stages of every leukemic, is treated by accessory methods, such as blood transfusions and arsenic, liver extract and ventriculin.

Summary and Conclusions. The present study is based on an analysis of 2425 cases collected from the literature and of 129 cases personally observed. A rather close harmony was found in the different groups collected from leading institutions of various parts of the world and it may be said that irradiation forms the method of choice in all three types of lesions analyzed.

(*a*) In lymphosarcoma, the 5-year survival amounts to 30% and the 10-year survival or cure to at least 10% to 15%. In the remaining the expectation of life is increased from $2\frac{1}{2}$ to $3\frac{1}{12}$ years. The immediate results often are so prompt and decisive that they may be called "spectacular."

(*b*) In Hodgkin's disease, the 5-year survival reaches 15% to 33%, but the cases in the great majority remain carriers of the disease, necessitating frequent resumption of the irradiation. A 10-year survival or cure occurs in 8% of the cases or less. In those who died within the first 5 years, the average expectancy of life was increased from 2 to $3\frac{1}{2}$ years. The symptomatic improvement is nearly always marked but not so spectacular as in lymphosarcoma.

(*c*) No cure is believed to occur in leukemia as a result of the irradiation. The prolongation of the average life duration is

likewise rather insignificant, perhaps with $\frac{1}{3}$ to $\frac{1}{4}$ of the natural expectancy, which is considered to be about $3\frac{1}{2}$ years in the chronic forms of both the lymphatic and the myelogenous type. The symptomatic improvement, however, is remarkable and it is believed that the efficiency of the patient is increased at least 60% throughout the major part of the duration of the disease. In the acute forms of leukemia not even a temporary improvement is observed.

The results of teleroentgen therapy which was started a few years ago are not included in this article, but it is believed that they will not materially influence the above data. Likewise little improvement in the results is expected from the introduction of the Roentgen ray therapy with voltages above 200 kv., except perhaps in certain well-selected cases of localized lymphosarcoma where a higher penetration is needed.

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THE SYNDROME OF ACUTE AGRANULOCYTOSIS AND ITS OCCURRENCE AS A COMPLICATION OF KALA-AZAR.

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Agranulocytosis and malignant or idiopathic neutropenia are terms which have been used interchangeably to designate a relatively rare type of severe leukopenia which is chiefly characterized by an absence of, or a very marked decrease in the relative number of polymorphonuclear granulocytes in the blood. This condition is not to be confused with simple leukopenia, a common state accompanying many diseases such as pernicious anemia, malaria, typhoid fever, and others. In these latter diseases there occurs frequently both an absolute and a relative decrease of polymorphonuclear leukocytes, but this decrease is not marked and is of significance as a diagnostic rather than as a therapeutic indicator.

Leukopenia of a chronic type and of a moderately severe grade with leukocyte counts of from 1500 to 5000 cells per c.mm. and with granulocytes of from 20% to 60% is the rule in kala-azar. Acute agranulocytosis, on the other hand, has not been reported as a complication of the disease.

During the 8-month period from October, 1932, to June, 1933, there came under our observation 26 consecutive patients who were proved to have kala-azar. Of these, 4 exhibited agranulocytosis as a complication of the disease. Because of the close similarity of these attacks of acute agranulocytosis to those of idiopathic agranulocytic angina and because of the therapeutic problems involved we believe it is pertinent to report these cases in some detail.

Case Reports. Case 1.—W. H. T. (No. 40207), a male college student, aged 20, was admitted to the general medical service of the hospital on May 4, 1933, because of fever of 2 weeks' duration. Onset was gradual. Fever was accompanied by chilly sensations and general malaise. Slight epistaxis was noticed on the first day. Past and family histories were irrelevant, except that 1 of patient's siblings had had attacks of the schizophrenic type.

Physical examination on admission showed few positive findings. The skin and mucous membranes were pale. The liver was barely palpable. The spleen was 15 cm. below the costal margin. Aside from a few dental fillings, the rest of the physical examination was not important.

Laboratory findings on admission were as follows: Urine, normal.

Stool, normal except for the presence of ova of ascaris. Blood, red blood cells, 4.44 millions per c.mm., with 9.4 gm. hemoglobin; the white blood cells were 1350 per c.mm., with 48% granulocytes.

The diagnosis of kala-azar was proved by recovery of Leishman-Donovan bodies from the spleen and from the marrow of the sternum. Neostibosan,* 2.75 gm., divided into 11 doses, was given intravenously. The first 4 injec-

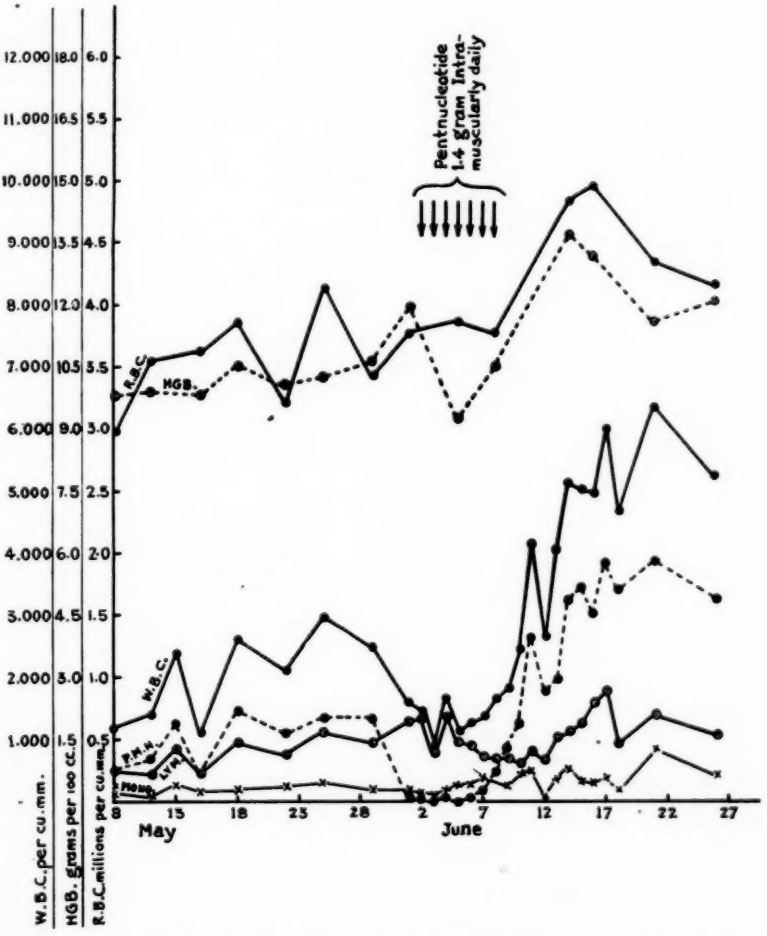

FIG. 1.—Case 1. Showing the fluctuations in blood cells and a period of acute agranulocytosis.

tions were given every day. The subsequent doses were administered every second day. During the first 3 weeks of treatment, patient showed noticeable clinical improvement, although the anemia and leukopenia persisted (Figs. 1 and 2). The polymorphonuclear neutrophils varied from

* Neostibosan-p-amino-phenyl stibinate of diethylamin, containing antimony in the pentavalent form.

44 to 56%. On May 29, 3 weeks after the beginning of the treatment, 1 day before the last injection was due and after 10 days of normal body temperature, patient had diarrhea without blood or mucus in the stool. Only a few white blood cells were seen when the stool was examined under the microscope. Blood studies done on this day showed no appreciable

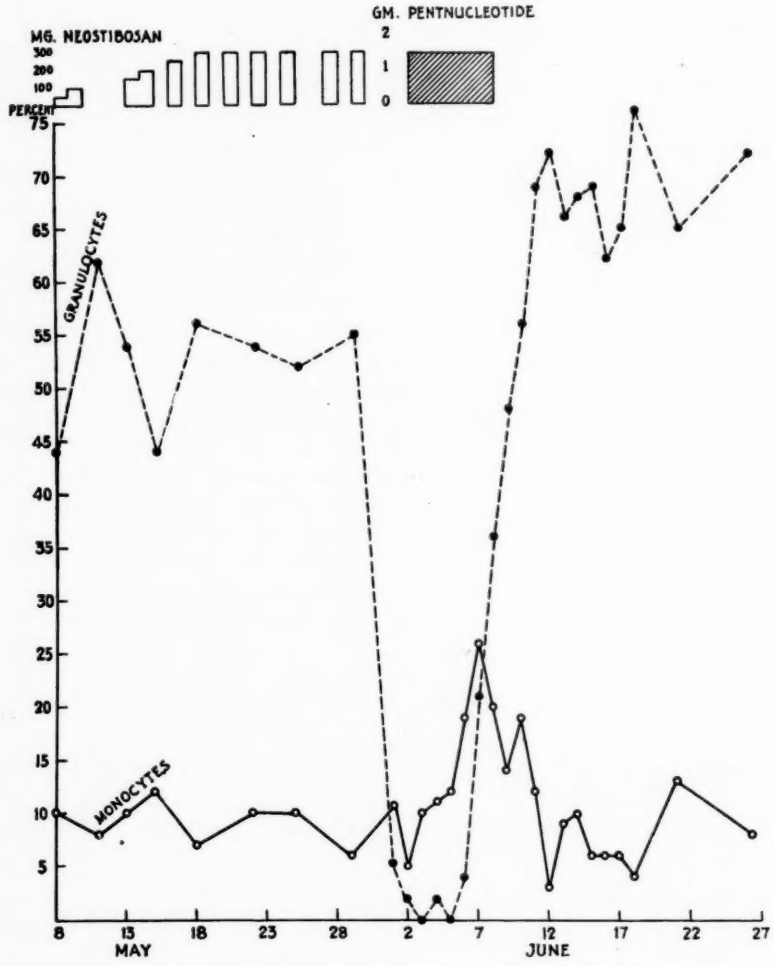

FIG. 2.—Case 1. Showing the dramatic changes in relative values of granulocytes and monocytes.

changes (red blood cells, 3.44 millions; hemoglobin, 10.6 gm.; white blood cells, 2450, with 55% granulocytes). Diarrhea continued and on May 31 there was fresh blood in the stool. On careful questioning the patient stated that he felt more ill and that he experienced a sense of fatigue and exhaustion. The next day a drop in the total count of the granulocytes was observed (total white blood cell count, 1550; granulocytes, 5.3%).

On June 2, 4 days after the onset of the diarrhea, and the second day after the rapid decrease of granulocytes was discovered, the body temperature was raised to 38.6° C. (total white blood cell count, 1450; granulocytes, 1%).

During the next few days the granulocytes completely disappeared from the peripheral blood and the patient was critically ill with sustained high body temperature (Figs 1 and 2). A few small shallow ulcers were seen on the buccal mucous membrane on the fourth day of the agranulocytosis and there was enlargement of the regional lymph nodes. The diarrhea, however, subsided. As soon as the acute agranulocytosis was discovered, antimony was withheld and pentnucleotide,* 0.7 gm., was given intramuscularly twice daily for 7 successive days. At about the height of fever, the fifth day of the agranulocytosis, the patient became mentally disoriented, and a diagnosis of toxic psychosis was made. With the increase of the granulocytes in the peripheral blood, which was evident from the fifth day of treatment with pentnucleotide, patient's body temperature came down and all signs of infection of the mucous membrane disappeared. Mental condition was also improved.

Blood cultures, on May 14, June 6 and 9, were all sterile. Stool cultures for pathogenic organisms were negative on 6 occasions, while 3 examinations for protozoa and ova after the onset of the diarrhea were negative. Wassermann and Kahn blood reactions were negative.

Summary. A patient with early kala-azar treated with Neostibosan developed agranulocytosis near the end of the course of treatment. No evidence of sepsis. The disease picture was complicated by the development of a psychosis. Treatment with pentnucleotide given. Improvement in the blood and clinical pictures occurred.

CASE 2.—H. C. F. (No. 37879), a male college student, aged 28, was admitted to the general medical service of this hospital on October 25, 1932, with history and physical and laboratory findings of kala-azar. The characteristic history dated back to 9 months, with insidious onset and gastro-intestinal disturbances.

On admission, the red blood cells were 2.35 millions; hemoglobin, 7.05; and 1600 leukocytes (61% were granulocytes) (Figs. 3 and 4).

The patient was treated with Neostibosan intravenously. A total of 3.05 gm., divided into 13 injections, was given during a period of 3 weeks. The body temperature gradually came down to and stayed at normal levels until November 21, after the patient had received the 13th injection, when it rose to 39° C. During the whole course of the disease the patient stated repeatedly that he felt very tired. Prior to the rise in body temperature this feeling of exhaustion was intensified. The patient complained of sore throat, but examination of the throat showed only some congestion. For the next 6 days there was agranulocytosis (Figs. 3 and 4), and patient was critically ill, with body temperature remaining above 39° C. No ulcers were seen in the mouth. The submaxillary lymph nodes were enlarged and tender. On November 24 there was a furuncle on the bridge of the nose and another on the lobe of the left ear. On November 25, 5 loose stools were passed, whereas until this time the patient had been constipated. Stools were black, contained mucus, many white blood cells and a few red blood cells. Patient was transfused twice, on November 26 and 29, with 400 cc. of whole blood each time. With the improvement in the blood picture, the superficial infections gradually healed and had disappeared on November 29. The next day the body temperature became

* Pentnucleotide—a mixture of sodium salts of pentose nucleotide prepared from the ribonucleic acid of yeast.

normal. The recovery was uneventful, although the patient had a protracted convalescence.

Summary. A patient with clear-cut kala-azar, treated with Neostibosan, developed transient agranulocytosis at about the end of treatment. Had superficial infection of the skin and enlargement

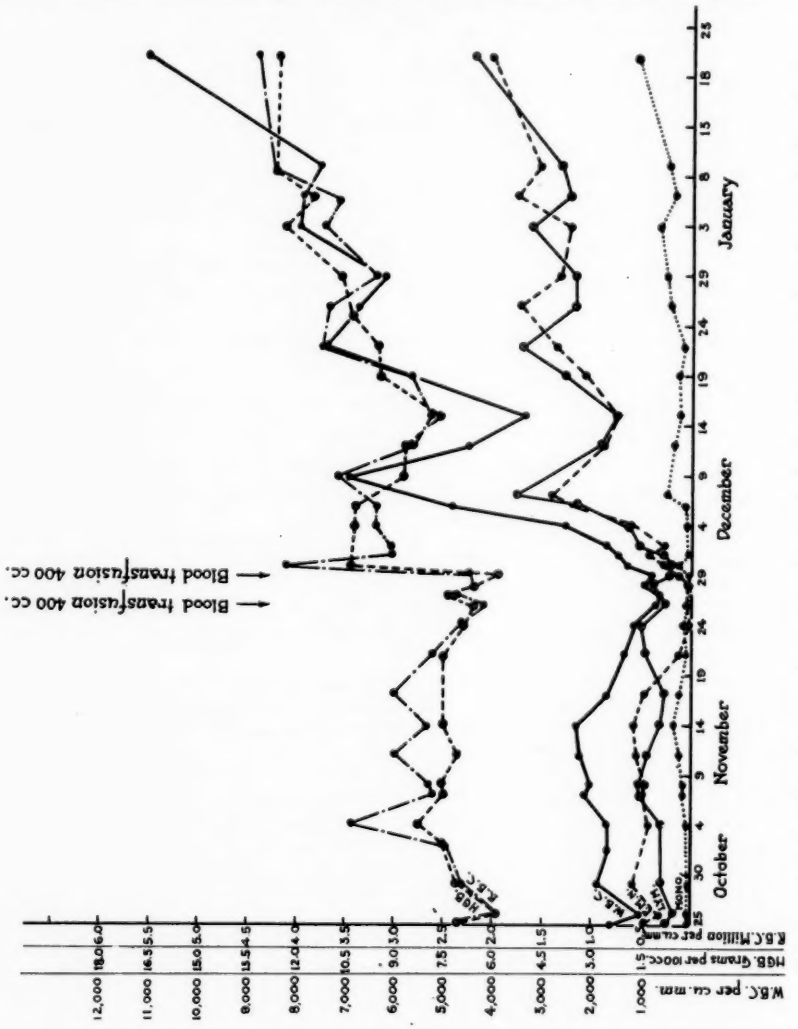

FIG. 3.—Case 2. Showing transient agranulocytosis during the course of studies on the blood cells.

of the cervical lymph nodes without evidence of sepsis. Two blood cultures and 5 stool cultures were negative. Transfused with whole blood. Recovery.

Comment on Cases 1 and 2. These 2 cases present certain features in common. On admission both patients had moderate leukopenia.

Both were treated with the same compound of antimony, Neostibosan. In both, a state of agranulocytosis was discovered 1 day before the last injection was due. Both were progressing satisfactorily when the agranulocytosis developed. The granulocytes of the blood were totally absent in Case 1, a few were present in

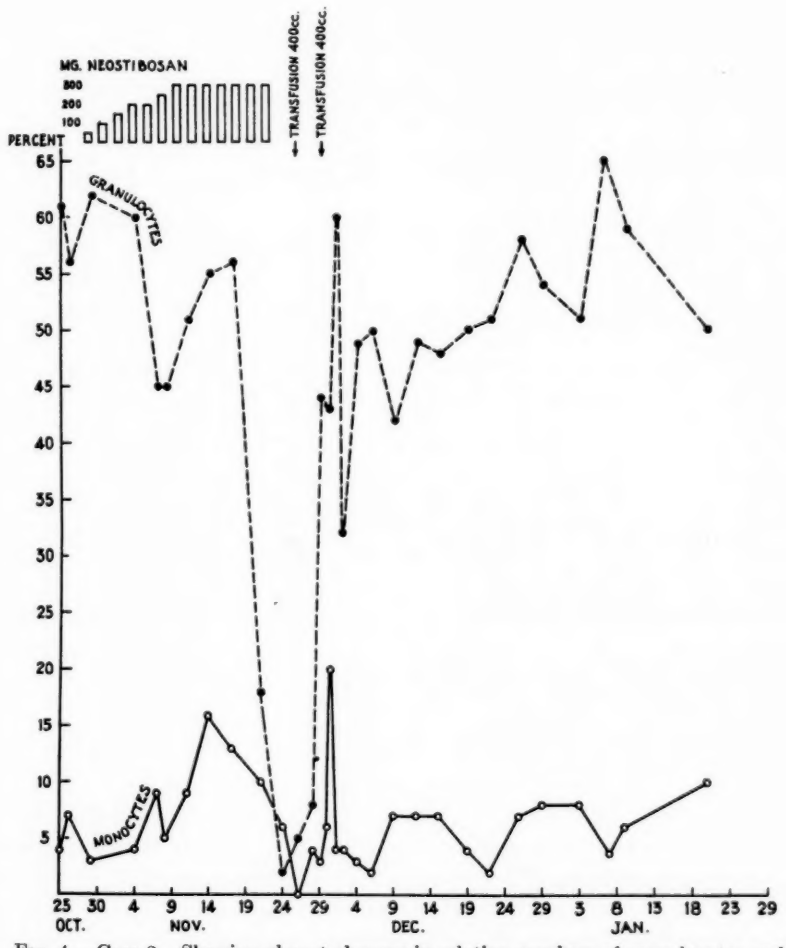

FIG. 4.—Case 2. Showing abrupt changes in relative numbers of granulocytes and monocytes.

Case 2. In neither was there any evidence of sepsis. Both patients had slight superficial infection with enlargement of the cervical lymph nodes, coming on after the onset of agranulocytosis. Both had some intestinal symptoms and signs, simple diarrhea in Case 2 and suggestive dysentery in Case 1. Pentnucleotide was given in Case 1 while blood transfusion was resorted to in Case 2. Both

patients had increases in the total white blood cell counts and percentages of granulocytes after the 5th day of the agranulocytosis. Both recovered from the transient agranulocytosis.

CASE 3.—C. M. M. (No. 38709), a female baby, aged 11 months, was admitted to the pediatric service of this hospital because of high fever of 2 weeks' duration. Past and family histories were irrelevant. On admission the important physical findings were: (1) Moderately enlarged and

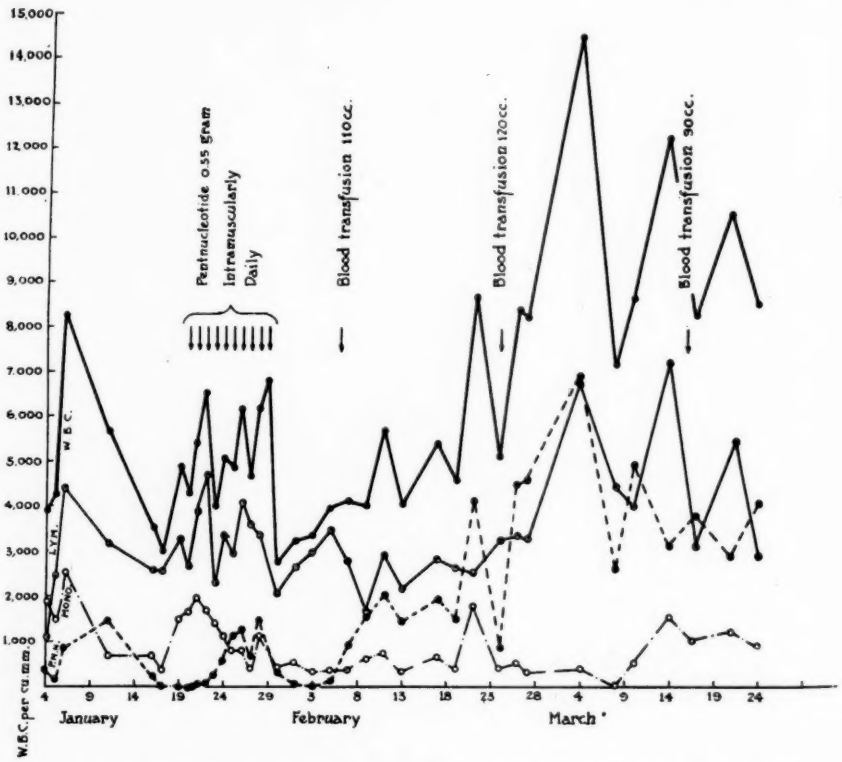

FIG. 5.—Case 3. Showing recurrent agranulocytosis. Only the total white blood cell and differential counts are given. The hemoglobin values and the red blood cell counts did not show any significant change except as results of blood transfusions.

injected tonsils; (2) palpable but non-tender cervical lymph nodes; (3) a small ulcer at the tip of the tongue; and (4) liver 3 cm. below the costal margin in the right midclavicular line. The spleen was not palpable.

The blood showed moderately severe anemia (hemoglobin, 6.9 gm.) and moderate leukopenia (total white blood cell count, 3900). Differential white blood cell count showed only 9% neutrophils, while the monocytes were as high as 48%.

The patient's course in the hospital was as follows:

January 3 to 16, there was no change in the general condition; had a low-grade fever.

January 17 to 21, corresponding to the period of agranulocytosis (Figs. 5

and 6), there were high body temperature, reaching 40.6° C., swollen gums and enlarged and tender cervical lymph nodes.

January 22 to 31, improvement in blood and clinical pictures, but low-grade fever persisted.

February 1 to 6, agranulocytosis and high fever recurred. Smear of material obtained by puncture of liver showed a few Leishman-Donovan bodies. Spleen became palpable. There was again enlargement of the cervical lymph nodes. There was seen in the throat a white membrane,

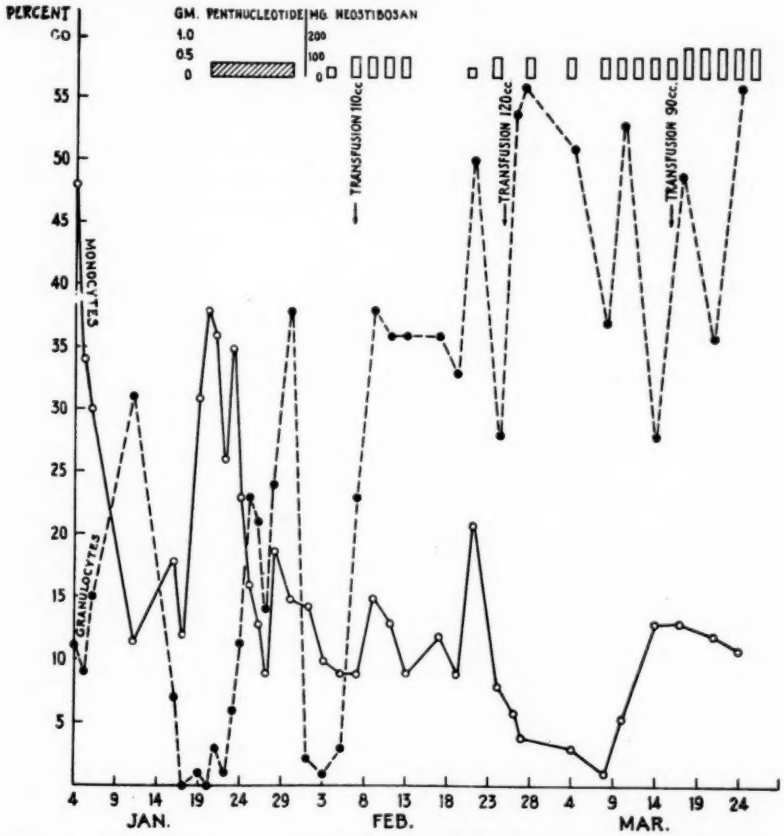

FIG. 6.—Case 3. Showing marked fluctuations in the percentage values of granulocytes and monocytes.

not unlike that found in diphtheria. Smear from the membrane showed B. diphtheriæ, and patient was given 20,000 units of antitoxin intramuscularly.

February 9 to 12, membrane in the throat showed no progress.

February 13 to 17, fever and a rash appeared, which were diagnosed as serum sickness.

February 20, lesions in throat healed.

Blood transfusions in small amounts were given 3 times, with a total of 320 cc. of citrated blood. Treatment with Neostibosan was started on

February 3. Three blood cultures done at different intervals were all negative. Patient was discharged from the hospital on March 29, well, after receiving a total of 2.05 gm. of Neostibosan.

Summary. An infant suffering from early kala-azar and without any treatment showed cyclic changes in the number of the granulocytes in the peripheral blood. These fluctuations were accompanied by appearance and disappearance of ulceration of the mucous membrane and rise and fall of the body temperature. Such changes were not observed after the institution of treatment for kala-azar. No evidence of sepsis. Recovery.

Comment on Case 3. The spontaneous cyclic changes in the number of the granulocytes in the peripheral blood is of interest. During the period of observation the granulocytes were absent on 2 occasions during 1 month. With the agranulocytosis there were elevation of the body temperature and ulceration in the mouth or throat with enlargement of the regional lymph nodes. The exact time relationship between the two was not clear-cut since daily blood counts were not done. Attention is called to the fact that the total white blood cell count was never below 2500. On one occasion it was 4850 when the percentage of granulocytes was zero. This agranulocytosis was no longer observed after treatment with antimony was started. On several occasions after the beginning of recovery there occurred leukocytosis.

CASE 4.—L. W. C. (No. 37685), a boy, aged 9½, was admitted to the pediatric service of this hospital, on October 10, 1932, because of irregular fever, distention and a mass in the left upper quadrant of the abdomen for 7 months, general anasarca for more than 1 month and dyspnea, palpitation of heart and slight productive cough for 1 week. No mention was made of bleeding from any source. Past and family histories were not important.

On admission, patient was found to be very ill, with marked subcutaneous edema and ascites. There was light bleeding from the gums, with beginning noma. The bases of the lungs were compressed and the heart was displaced upward. The spleen was 14 cm. and liver 2 cm. below the costal margin in the midclavicular lines.

The laboratory findings on admission were as follows: Urine and stool showed no important abnormal changes. Blood: red blood cells, 2.66 millions; hemoglobin, 7.1 gm. per 100 cc. of blood; white blood cells, 800. Differential white blood cell count showed complete absence of granulocytes. These counts were confirmed repeatedly.

Smear of the material obtained from puncture of the spleen 2 days after admission showed numerous Leishman-Donovan bodies. Two days later the patient suddenly died of respiratory failure.

Necropsy confirmed the clinical findings and the diagnosis of kala-azar. Because of the agranulocytosis, the blood-forming organs were of special interest. The spleen was tremendously enlarged (1060 gm.) and very soft in consistency. Its surface was smooth and bluish-gray in color. There were several deep notches along the medial margin. On section the surface was slightly swollen, with edges slightly everted. The pulp was grayish-red in color and a moderate amount of it could be scraped away. Neither the lymph follicles nor the trabeculæ were visible, the surface being homogeneous in appearance. Microscopic examination of the sections revealed

large numbers of phagocytic cells scattered everywhere which contained many Leishman-Donovan bodies (Fig. 7). In the pulp there were also large numbers of small and medium-sized plasma cells, numerous small lymphoid cells and a few large lymphoblasts. The follicles contained fewer of the parasitized cells. Occasional follicles showed areas of scar tissue.

The bone marrow of the ribs and vertebræ was dark red. The entire cavities of the femur and fibula on one side were filled with fairly solid, red marrow. Microscopically the marrow was very cellular. It showed large numbers of macrophages, containing many Leishman-Donovan bodies (Fig. 8). There was also some phagocytosis of red blood corpuscles by the macrophages. There were fair numbers of medium-sized cells having rounded nuclei and weakly acidophilic cytoplasm, among which a few mitotic figures were present. Very few late myelocytes and mature leukocytes could be found. Few eosinophilic leukocytes were present. The marrow was indeed poor in granulocytes. Plasma cells and small lymphoid cells were quite numerous. Megakaryocytes were present. Nucleated red cells were not conspicuous, although all stages in development could be seen.

There was moderate to slight general lymph node enlargement and many of the nodes were dark red in color. This redness was due to congestion in the blood capillaries and hemorrhage into the lymph sinuses. There was moderate hyperplasia of the reticuloendothelial cells and of the young lymphoid elements. Numerous plasma cells were present. No Leishman-Donovan bodies could be found either in the lymph nodes or the tonsils. This was surprising in view of the heavy infection in the spleen and bone marrow.

Summary. An advanced case of kala-azar in a boy of 9. There were extreme leukopenia and total absence of granulocytes in the peripheral blood. Period of observation was short. The post-mortem findings showed tremendous proliferation of macrophages which had ingested the Leishman-Donovan bodies. The bone marrow was poor in granulocytes.

Comment on Case 4. From clinical, laboratory and necropsy findings it is certain that this is a case of kala-azar. The extreme leukopenia and total absence of the granulocytes are remarkable. Strong[1] mentioned the fact that the reduction of neutrophils in kala-azar in children is more marked than in adults, for these cells may be decreased to 5% of the total white blood cells. It is interesting to note that the smears obtained from antemortem puncture of the spleen and the sections of the spleen and bone marrow were packed full of big, phagocytic cells which contained the causative agent of kala-azar. Hu and Cash[2] suggested that the anemia in kala-azar is myelophthisic in the sense that there is a crowding out of the blood-forming tissue by the tremendous increase of macrophages. We may speculate here that the extreme leukopenia and the total absence of the granulocytes from the peripheral blood may be, at least in part, the result of this process.

Treatment of Acute Agranulocytosis. The treatment of acute agranulocytosis occurring as a complication of kala-azar or of pyogenic infection, or as a part of the disease agranulocytic angina, is

unsatisfactory. The mechanism of the development of agranulocytosis is not known and there is no specific therapy. It is always a problem whether or not to give transfusions of blood. It is not generally accepted that in agranulocytic angina they decrease the mortality significantly. In untreated cases of agranulocytic angina the mortality is about 75%, whereas 64% of patients treated by means of transfusions of blood die.[3] It is conceivable that transfusions of large amounts of blood may act to depress the development of granulocytes in the bone marrow and, therefore, may be contraindicated.

Exposures to small doses of Roentgen rays have been used in the treatment of agranulocytic angina by several investigators, notably by Friedemann and Elkeles.[4] The collected series of cases by Taussig and Schnoebelen[3] reveal a mortality of 53% when this treatment was used. The administration of diphtheria antitoxin, antistreptococcus serum, injections of foreign proteins, of neoarsphenamin, of liver extract and the use of various other remedies have their adherents, but the cases treated have been so few and so inadequately controlled that one cannot properly evaluate the advantages or disadvantages of such procedures.

It has been known for many years that the administration of nucleic acid and some of its derivatives to animals will bring about an increase of neutrophils in the blood. Reznikoff[5] has recently reported that certain derivatives of nucleic acid, the purine bases, adenin and guanin, when given intravenously to patients suffering from agranulocytosis, have the power of raising the peripheral neutrophil count. With such treatment, fully described by the author, a mortality of only 27% is reported in a series of 35 cases.

Jackson, Parker, and Taylor[6] have utilized another derivative of nucleic acid designated Pentnucleotide. In a series of 54 patients they experienced a mortality of 30%.

We have treated 2 of our cases of acute agranulocytosis complicating kala-azar by intramuscular injections of Pentnucleotide, with satisfactory results in 1 (Case 1) and no apparent effect in the other (Case 3).

It would appear from the above data that the administration of pentose nucleotide or of purine bases derived from nucleic acid offers by far the most satisfactory treatment not only for agranulocytic angina, but also for conditions of agranulocytosis the result of pyogenic infection or of chronic benzene poisoning. For details concerning the administration of these drugs the papers referred to should be consulted.

There are certain other points in the general and local treatment of patients suffering from agranulocytosis which have been found of value and are tabulated below:

1. Strict respiratory isolation from the onset. All attendants or visitors having recent respiratory infections should be excluded.

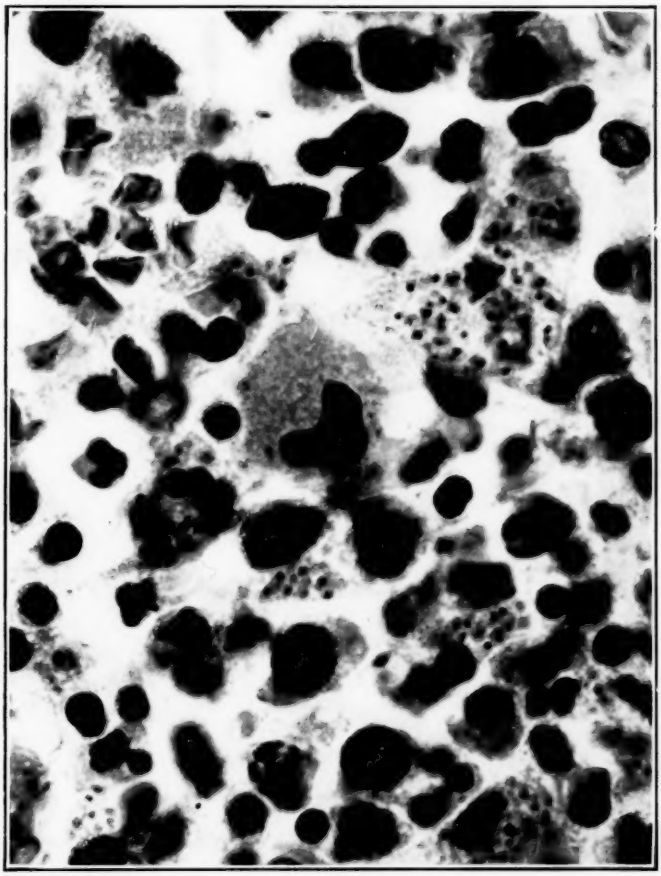

FIG. 7.—Case 4. Photograph of section of spleen showing large number of Leishman-Donovan bodies within macrophages. (× 1290.)

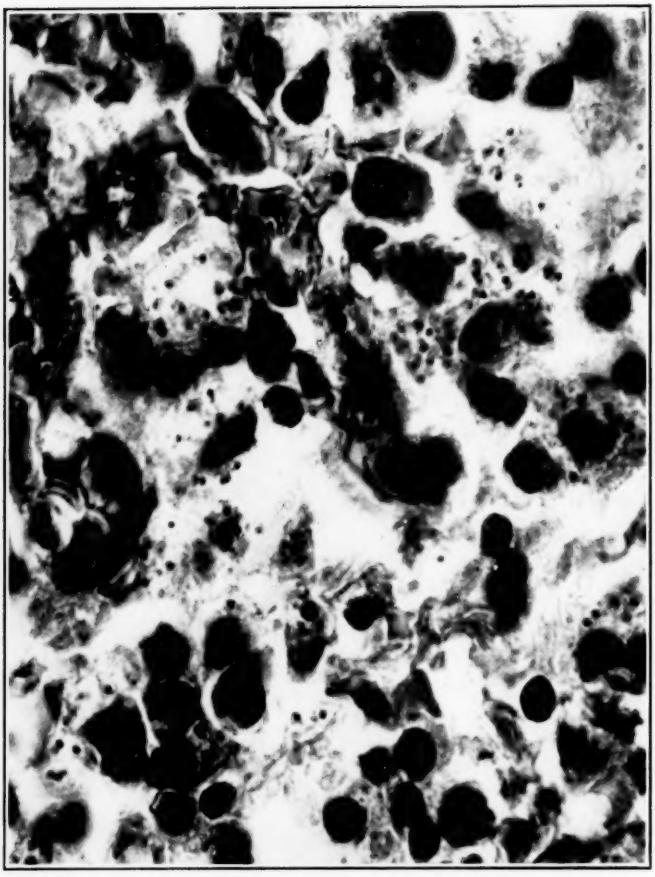

FIG. 8.—Case 4. Photograph of section of the bone marrow of the rib showing many Leishman-Donovan bodies within macrophages. (× 1290.)

2. If the attack is associated with treatment by means of drugs (antimony, arsphenamins), such medication should be withheld.

3. Liquid or very soft solid diet containing generous amounts of cod-liver oil, orange juice and other essential food factors should be the diet of choice.

4. Fluids should be taken in liberal amounts.

5. Mild cleansing mouth washes at frequent intervals. The alternate use of hydrogen peroxid (1.5% to 3%) and of saturated solution of sodium perborate is recommended.

6. Frequent painting of lesions of the mucous membranes with aqueous solution of gentian violet (1%) seems to be of value.

Although little is known concerning the etiology or the specific treatment of agranulocytic angina or of acute agranulocytosis of other origin, it appears that appropriate therapy with derivatives of nucleic acid may be a life-saving procedure.

Discussion. The condition of acute agranulocytosis as observed in the above cases is not merely an exaggeration of the usual state of leukopenia in kala-azar. It occurs as an unexplained phenomenon characterized by an abrupt and transient disappearance or marked decrease of the polymorphonuclear cells from the blood. This complication apparently bears no relation to the existing state of anemia or leukopenia. Neither does the relative number of neutrophils existing in the blood prior to or after the subsidence of an attack of acute agranulocytosis have any apparent relation to the episode.

Attention is called to a case reported by Tso[7] which differed from 3 of the cases studied by us in that the latter exhibited acute agranulocytosis, whereas Tso's case represented a more chronic and usually less severe granulocytopenia which, as Strong[1] pointed out, occasionally occurs in children afflicted with kala-azar. The period of observation in our fourth case was too short to ascertain whether there existed acute or chronic agranulocytosis. It would appear from our studies that acute agranulocytosis in kala-azar is much more common than is ordinarily supposed. This may have some bearing on another complication of kala-azar, namely, noma or cancrum oris, which not uncommonly occurs in patients suffering from this disease. It is conceivable that during the phase of acute agranulocytosis, which is unrecognized and untreated, the resistance of the patient is so lowered that the appearance of noma as in our Case 4 with its rapid and extensive ulceration of the tissues is rendered possible.

Agranulocytosis, in our experience, has been observed only in a few diseases. It is rare in aplastic anemia and in leukemia and is uncommonly encountered in the course of pyogenic infections, but occurs as the chief characteristic of the disease agranulocytic angina (Fig. 9). The agranulocytosis occasionally found associated with aplastic anemia and with leukemia usually is gradual in onset

and is associated with a marked disturbance in the formation of all the structural elements which have their origin in the bone marrow. On the other hand, agranulocytosis, as it occurs in agranulocytic angina or during the course of kala-azar or associated with pyogenic infections, is acute in onset and usually is short in duration, terminating rapidly in death or recovery. The age and sex incidence of agranulocytosis other than agranulocytic angina is not remarkable, whereas in the latter disease the sex is preponderantly female and the age is usually near that of the menopause.

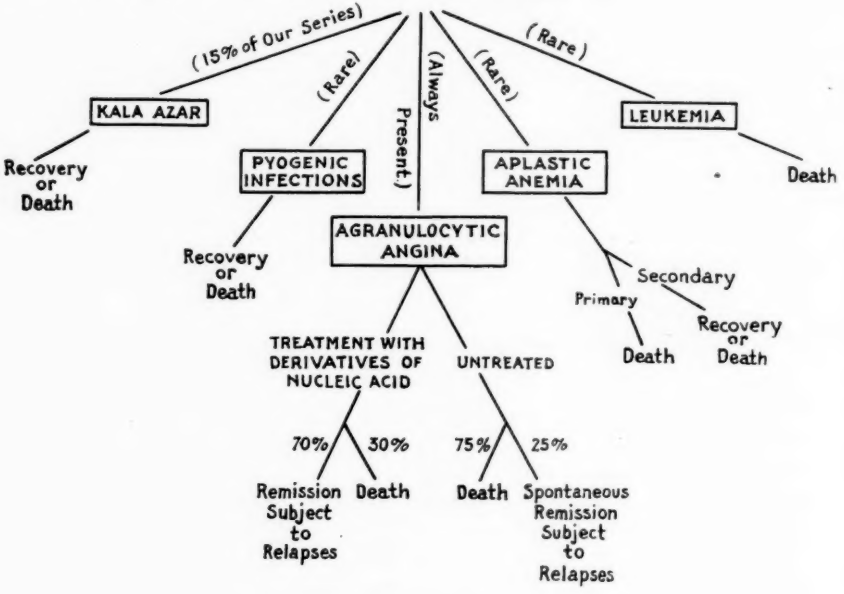

FIG. 9.—Occurrence of agranulocytosis.

The symptoms and clinical course of acute agranulocytosis as encountered in kala-azar and in certain rare cases of pyogenic infection are strikingly similar to those of idiopathic agranulocytic angina. Roberts and Kracke[8] have followed the changes in the number of granulocytes preceding and during attacks of agranulocytic angina. They found that increasing leukopenia occurred about 4 days prior to the onset of the classical clinical symptoms and signs of the disease and that collapse may occur associated with the continued absence of the granulocytes from the blood. One of us[9] has observed in 2 cases of recurrent agranulocytic angina that increasing leukopenia with decrease of granulocytes often is the first manifestation of the relapse. However, if the patient is questioned carefully at this early phase of the disease, it is usually found that there exists an unexplained feeling of fatigue and weak-

ness. These symptoms become more intense as the degree of agranulocytosis increases and as its duration is prolonged.

The occurrence of acute agranulocytosis in patients under observation suffering from kala-azar has rendered possible further observations on these early symptoms and signs associated with the disappearance of granulocytes from the blood. Such observations have led us to the concept that there is a characteristic syndrome which may be associated with acute agranulocytosis (Fig. 10). This

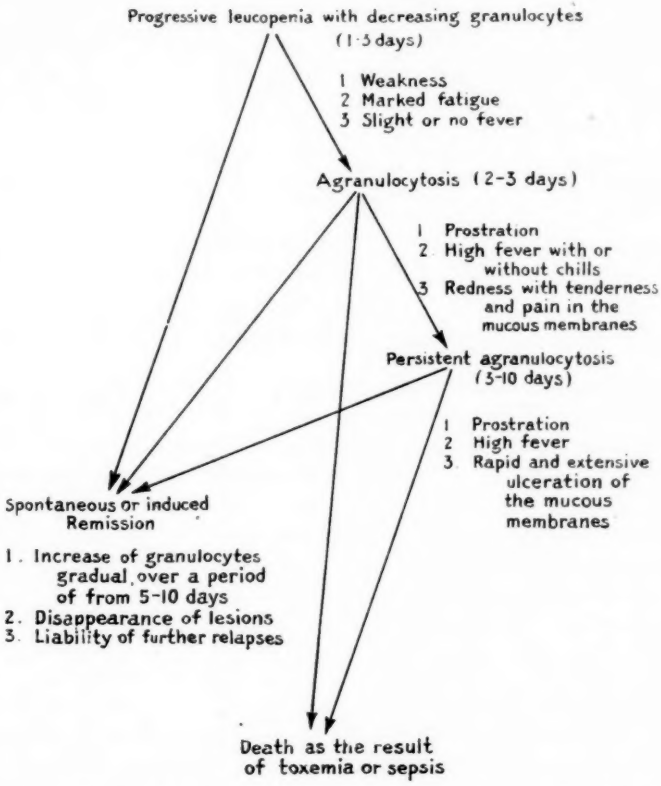
Progressive leucopenia with decreasing granulocytes
(1-5 days)
1 Weakness
2 Marked fatigue
3 Slight or no fever
Agranulocytosis (2-3 days)
1 Prostration
2 High fever with or without chills
3 Redness with tenderness and pain in the mucous membranes
Persistent agranulocytosis
(5-10 days)
1 Prostration
2 High fever
3 Rapid and extensive ulceration of the mucous membranes
Spontaneous or induced Remission
1. Increase of granulocytes gradual, over a period of from 5-10 days
2. Disappearance of lesions
3. Liability of further relapses
Death as the result of toxemia or sepsis

FIG. 10.—Syndrome of acute agranulocytosis as it occurs in agranulocytic angina, kala-azar and pyogenic infections.

syndrome is less conspicuous when it occurs as a complication of kala-azar than when it is associated with agranulocytic angina owing to the fact that attacks of the latter disease come on abruptly during a period of good health whereas the agranulocytosis of kala-azar occurs in patients who are already quite ill.

The first clinical manifestations of this syndrome are weakness and a feeling of exhaustion coming on rather rapidly over a period of from 12 to 72 hours. White blood cell counts at this period show

an increasing leukopenia with a decrease in number of granulocytes. The symptoms become more intense and the leukocytes frequently decrease to from 500 to 2000 cells per c.mm. with a total absence of, or the presence of very few neutrophils. After from 24 to 96 hours more alarming symptoms appear, consisting of high fever, redness and tenderness of the mucous membranes, soon followed by rapidly extending ulceration accompanied by localized pain and marked general discomfort. Unless there occurs, either spontaneously or as the result of treatment, an increase in the number of neutrophils, the symptoms and signs progress and the patient succumbs often as the result of infection. On the other hand, if the leukopenia subsides and the granulocytes progressively increase before severe secondary infection has occurred, a remission takes place in which there is rapid recovery.

The fact that in 2 of our cases acute agranulocytosis occurred during the course of treatment with Neostibosan and after the administration of a considerable amount of the drug suggests that the medication might have played some part in the precipitation of the attack. Recently 2 additional cases of acute agranulocytosis of kala-azar not reported in this communication, but which were comparable to Cases 1 and 2, have occurred.* The agranulocytosis in 4 of the 6 cases came on acutely near the end of the proposed course of treatment with Neostibosan. Because of this theoretic implication we have studied in animals the effects on the blood and blood-forming organs of large and repeated doses of Neostibosan and urea stibamin.† The report of this work will be published elsewhere, but it may be stated here that no significant changes could be demonstrated in the blood of these animals. Further studies of additional cases may give some clue as to the etiology of the agranulocytosis, but at present no satisfactory explanation is available.

Summary. Agranulocytosis occurred in 4 of 26 consecutive patients suffering from kala-azar. In 3 of these the agranulocytosis was acute, in 1 of which it was recurrent. The period of observation of the fourth case was too short to determine whether the attack was acute or chronic. Two additional cases were observed, but not reported in detail.

Acute agranulocytosis is a common and previously unrecognized complication of kala-azar. It is only as the result of frequent and careful studies of the blood that this complication may be detected and appropriate treatment given.

The treatment of acute agranulocytosis is discussed.

* Since the preparation of this manuscript 2 additional patients have been observed in whom acute agranulocytosis has occurred as a complication of kala-azar. One of these 2 patients died during the attack on the 4th day of the agranulocytosis and in spite of vigorous treatment with Pentnucleotide.

† Urea stibamin—carbamid salt of p-amino-phenyl stibimic acid containing antimony in the pentavalent form.

A syndrome of acute agranulocytosis as it occurs in kala-azar, pyogenic infections and agranulocytic angina is described.

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HEART DISEASE IN THE MIDDLE WEST.*

(Incidence and Etiology of 1646 Cases at the Cook County Hospital.)

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Surveys of the incidence and etiology of the various forms of heart disease have been reported from a number of centers, but no detailed study has been made in the Middle West. Carr,[4] in a brief summary of the files of the Cook County Hospital, reported that, in 1923, there were 1236 cases of cardiac disease with 325 deaths. Gethner,[8] without submitting statistics, said that in Chicago, where everyone is under unusual strain, the increase in mortality from cardiovascular disease is 1½ times greater than that of the whole United States. In 1932, the death rate was 1090 per 100,000 population for the United States registration area.[11] Heart disease led all causes and accounted for 19.2% of the deaths. Riesman,[11] in summing up the heart situation recently, stated that whether or not there is an alarming increase in deaths from organic heart disease, the fact that heart disease stands at the head of the list makes it a definite problem in health conservation in the sense that efforts should be made to postpone as late as possible death from this cause.

This study covers a period of 18 months, from January 1, 1932, to June 30, 1933. The list of patients entering the Cook County Hospital under the diagnoses of organic heart disease, decompensated heart, auricular fibrillation, coronary sclerosis, mitral stenosis, endocarditis and similar cardiac diagnoses was obtained each day from the cards in the Admitting Room. Each patient was

* Work done while an intern at the Cook County Hospital, Chicago, Ill.

followed up as soon as possible to ascertain whether the diagnosis was correct. Practically all were submitted to individual study during the stay in the hospital. These figures represent only the incidence and etiology of heart disease in patients admitted to the Cook County Hospital. During this period, 235,193 patients applied for admission to the hospital and 95,629 (40%) were admitted. In this group of admissions, 4600 (4.8%) entered with a cardiac diagnosis. A follow-up of these 4600 cases in the hospital, along with the locating of cardiacs in the wards with a non-cardiac admitting room diagnosis, revealed that only 1646 (1.7%) patients had definite organic heart disease. It is well to emphasize that these 1646 patients were admitted 2800 times to the hospital during the 18-month period. The criteria followed for the classification and diagnosis of heart disease were those approved by the American Heart Association.[18] Most of the criteria are definite except in cases which have a hypertensive or arteriosclerotic etiology. In this study all cases that presented clinically gross arteriosclerosis without hypertension were included in the arteriosclerotic group. Cases which presented evidences of myocardial insufficiency with hypertension and no clinical evidence of arteriosclerosis were included in the hypertensive group. All cases that presented both gross arteriosclerosis and hypertension were included in the group termed arteriosclerosis with hypertension. In this group it is very likely that the hypertension has no relation to the arteriosclerosis. These patients probably have outlived the hypertension and reach the stage where they develop arteriosclerosis. The term senescent or degenerative heart disease does not and should not include the hypertensive etiology. Hypertension appears to be a separate and distinct entity unrelated not only to arteriosclerosis but also to syphilis, rheumatic heart disease and to thyrotoxicosis.

TABLE 1.

General survey.	No. of patients and per cent.
Applied for admission	235,193
Hospital admissions	95,629 (40%)
Deaths, entire hospital	9,276 (9.7% of admissions)
Medical admissions	22,942 (24% of admissions)
Medical deaths	4,303 (19% of medical admissions)
Total hospital autopsies	1,898 (20% of all deaths)
Organic heart disease	1,646 (1.7% of all hospital admissions) (7.2% of medical cases)
Improved	971
Unimproved	53
Deaths	622 (6.7% of all deaths) (14.4% of medical deaths)
Autopsies	304 (16% of all autopsies)

Incidence of Heart Disease. The 1646 cases of organic heart disease were 1.7% of the total hospital admissions and only 7.2% of the medical cases, a low figure and certainly no cause for great alarm (Table 1). On discharge, 971 were improved, 53 unimproved

and 622 (38%) died in the hospital. This constituted 6.7% of all the hospital deaths from all causes and 14.4% of all the medical deaths. The basic cause for the high mortality was the economic situation of the patient. Many of these patients were discharged from the hospital well compensated and in good condition only to return within a month or 6 weeks in a terminal condition because they had to return to work to live or because they had no work and had great difficulty just living.

Age Incidence. Of the white patients, 52.1% were between 40 and 60 years of age. The common decades were the 6th for the white male and the 5th for the white female. Of the colored patients, 56.8% were in the 40-to-60-year group, but the 5th decade was the most common period for heart disease to occur in this group. Of the 1646 patients, 54% were in the 40-to-60-year group.

TABLE 2.—PERCENTAGE OF THE AGE GROUPS.

Ages.	White.				Colored.				Both.	
	M	F	T	%	M	F	T	%	Totals.	%
14–20 . .	19	15	34	2.9	5	3	8	1.7	42	2.6
21–30 . .	30	22	52	4.4	24	16	40	8.9	92	5.6
31–40 . .	87	48	135	11.1	54	30	84	18.3	219	13.1
41–50 . .	190	74	264	22.1	117	43	160	34.5	424	26.0
51–60 . .	305	49	354	31.0	82	21	103	22.3	451	28.0
61–70 . .	203	46	249	21.2	43	9	52	11.3	301	18.0
71–80 . .	72	13	85	7.2	12	0	12	2.6	97	5.8
81–90 . .	10	2	12	0.1	1	1	2	0.4	14	0.9
Totals . .	916	269	1185	100.0	338	123	461	100.0	1646	100.0

Etiologic Factors. The most common cause was hypertension, alone or in combination with another factor. Table 3 indicates that it was present in 57% of the cases; in 53.6% of the white patients and 60.4% of the colored patients. The 4 main groups, hypertensive, arteriosclerotic, rheumatic and syphilitic involvement, accounted for 90% of the cases; 88.4% of the white and 94.5% of the colored patients.

Arteriosclerosis. All of the 128 (7.2%) patients were 61 years and over, except 13 white males, 12 of whom were in the 51-to-60-year group and 1, the youngest, was 43 years of age. On discharge, 75 were improved, 4 unimproved and 49 died in the hospital. Twenty-four autopsies were performed. In spite of the advanced age of most of these patients the hospital mortality was only 39%.

Arteriosclerosis With Hypertension. Gross arteriosclerosis with blood pressure readings above 150/100 was found in 163 (9.9%). All of these patients, except 12, were above 61 years of age. Probably these patients have outlived the damaging effects of the hyper-

tensive state and reached the age where the arteriosclerotic changes began to manifest symptoms clinically. On discharge, 99 were improved, 7 unimproved and 56 died (34%).

Subacute Bacterial Endocarditis. There were 42 patients (2.7%) with this affection, although 2 patients had the endocardial infection other than of the valve. One had involvement of the left side of the interventricular septum with perforation into the right ventricle, and the other had a verrucous aortitis superimposed upon a syphilitic aortitis. The ages varied from 14 to 70 years. Four patients were discharged from the hospital, all after long periods of time. Thirty-eight patients died in the hospital (90%), with autopsies on 35.

TABLE 3.—PERCENTAGE OF ETIOLOGIC FACTORS IN THIS STUDY.

Probable etiology.	White.				Colored.				Both.	
	M	F	T	%	M	F	T	%	T	%
Arteriosclerosis	101	18	119	10.0	7	2	9	1.9	128	7.2
Arteriosclerosis with hypertension	118	15	133	11.1	27	3	30	6.6	163	9.9
Bacterial	22	10	32	2.9	3	7	10	2.1	42	2.7
Pulmonary emphysema	23	2	25	2.1	1	0	1	0.2	26	1.6
Hypertension	376	105	481	40.5	163	60	223	48.5	704	43.0
Rheumatism	134	81	215	18.3	20	23	43	9.4	258	15.8
Rheumatic with hypertension	6	3	9	0.7	3	2	5	1.0	14	0.9
Syphilis	75	2	77	6.5	92	12	104	22.8	181	10.9
Syphilis with hypertension	12	3	15	1.3	13	7	20	4.3	35	2.2
Thyrotoxic	18	18	36	3.0	2	6	8	1.6	44	2.6
Unknown	26	2	28	2.3	3	0	3	0.6	31	1.9
Miscellaneous	5	10	15	1.3	4	1	5	1.0	20	1.3
Totals	916	269	1185	100.0	338	123	461	100.0	1646	100.0

Pulmonary Emphysema. The etiologic factor appeared to be confined to the white patients as a cause of myocardial insufficiency. Of 26 patients (1.6%), only 1 was colored. In practically all of these patients the emphysema was the result of a dusty occupation over a period of many years. The hospital mortality was 50%, and autopsies were performed in 8 of the 13 cases.

Hypertension (Without Gross Arteriosclerosis). This factor accounted for 43% of the cases alone and was present in 57% of all the cases. On discharge, 448 patients were improved and 18 unimproved. There were 238 deaths (32%). Only 88 autopsies were performed which, if considered alone, would not give a true picture of the part hypertension takes in the etiology of heart disease.

Rheumatic Heart Disease. The largest number of these 258 patients (15.8%) were in the 4th decade. There were 76 deaths (30%) and autopsies were performed in 32 cases.

Rheumatic Heart Disease With Hypertension. This group of 14 patients were not unlike the above group except that the blood pressure readings were above 150/100. There were 6 deaths (43%), and autopsies confirmed the diagnoses.

Syphilitic Heart Disease. This appeared a decade earlier in the 104 colored patients than in the 77 white patients. On discharge, 78 patients were improved, 1 unimproved and there were 102 deaths (56%).

Syphilitic Heart Disease With Hypertension. This combined etiology, present in 35 cases (2.2%), had a mortality slightly lower than the previous group. There were 18 deaths (51%), and autopsies were performed in 15 cases.

Thyrotoxic. Forty-four patients (2.6%) presented cardiac symptoms and findings on a thyrotoxic basis; 13 patients died in the hospital (30%).

TABLE 4.—PERCENTAGE OF HEART DISEASE PREVIOUSLY REPORTED.

Hospital or city and year.	Hospital admissions.	Medical admissions.	Autopsy records.	%
Galveston, Texas,[13] 1920–1926	25,816	...	...	3.5
Massachusetts General,[15] 1926	8,226	...	...	6.0
		2,766	...	18.0
Cincinnati,[1] 1926	9,570	...	...	7.2
Pacific Northwest,[5] 1928	28,661	...	...	12.0
		13,258	...	26.0
Salt Lake City,[14] 1927–1930	16,519	...	...	2.9
Galveston, Texas,[12] 1927–1930	...	...	...	3.3
				16.3
Vanderbilt Univ. Hospital,[10] 1931	...	...	...	4.1
Cincinnati,[9] 1927–1931	...	...	2344	17.0
Detroit,[2] 1932–1933	...	...	1535	20.0

Thyrotoxic With Hypertension. Seven patients had hypertension in addition to the thyrotoxic heart disease. Neither factor seemed to have any relation to the other. Three patients were discharged as improved, 3 as unimproved and 1 male died in the hospital.

Unknown. In a group of 31 cases (1.9%) no known etiologic factor or factors were evident to account for the myocardial insufficiency. Five autopsies were performed of 8 deaths, and the etiology in these cases remained undisclosed. In all studied statistics of this type a small group of patients presented myocardial insufficiency to which no known etiologic factor could be attributed.

Miscellaneous. This included 4 cases of myocardial insufficiency attributable to anemia, 3 cases of congenital heart disease, 1 each of diphtheria, scarlet fever and toxic myocarditis, the 3 female patients with myxedema and the 7 patients previously mentioned

who had thyrotoxic myocarditis with hypertension. Only 1% of the cases of organic heart disease fall into this group.

Comment. For large general hospital admissions the incidence of organic heart disease varies from 1.7% for the Cook County Hospital to 12% for the Pacific Northwest. The latter figure is high, as Coffen[5] indicated, because hospital records are only satisfactory as to the incidence of cardiovascular disease as compared with the total medical admissions. The incidence was, of course, greater where only the medical admissions were considered, the lowest, 7.2%, at the Cook County Hospital and the highest was 26% from the Pacific Northwest.[5]

TABLE 5.—COMPARATIVE REPORTED PERCENTAGE OF ETIOLOGIC FACTORS.

Locality.	Arterio-sclerosis	Bac-terial	Hyper-tension.	Rheu-matic.	Syph-ilis.	Thyro-toxic.	Total cases.
Boston[3]	15.5	0	19.5*	46.4	10.6	0.1	600
New England[17]	23.1	0	0.1	44.5	9.0	0.0	1001
Virginia and Boston[16]	7.3	0	46.0	22.0	21.4	0.0	623
Galveston, Texas[13]	13.7	1.5	47.7	7.3	19.3	1.3	915
New England[15]	35.7	1.9	29.2	39.5	3.9	2.9	2421
Pacific Northwest[5]	...	...	56.0	1.0	...	6.1	3488
Salt Lake City[14]	21.1	0.2	14.9	44.0	1.1	9.3	867
Cincinnati[9]	41.0	9.0	...	3.0	14.0	...	398
Galveston[12]	20.2	...	57.2	...	12.7		
Detroit[2]	15.0	13.0	40.0	11.0	6.0	...	1535
New York State[6]	8.8	...	20.1	27.2	4.6	...	1934
Tennessee[10]	68.0†	...	68.0†	10.3	6.0	...	645
Washington, D. C.[7]	19.0	1.4	55.6	6.0	10.0	2.5	1200
Chicago (this study)	17.1	2.7	43.0	16.7	13.1	2.6	1646

* Classified as nephritic in the original study.
† Arteriosclerotic-hypertensive group combined.

The most common age group was the 40-to-60-year period. The average age was 53 years for the white patients and 44 years for the colored patients. There were a negligible number of patients between the ages of 14 and 20 years, but from this age upward the number of patients with heart disease gradually increased until it reached the peak in the 50-to-60-age group. In this decade, hypertensive and syphilitic heart disease were at their height, rheumatic heart disease took its toll of those that had suffered in the past decade and arteriosclerotic heart disease was beginning to manifest itself.

The outstanding etiologic factor in the causes of heart disease in the adult is hypertension. Comparative study of 14 such surveys from the United States give hypertension as the leading cause in 8 of the 14 reports. Rheumatic heart disease is given as the leading cause in 5 and arteriosclerotic heart disease in the other report. Three reports from the New England States[3,15,17] give rheumatic

heart disease as the leading cause, as do one each from the Rocky Mountain region[14] and the state of New York exclusive of New York City.[6] Arteriosclerotic heart disease, as the leading cause, is based on autopsy statistics from the Cincinnati General Hospital.[9]

The next important cause is arteriosclerosis and, with hypertension, is the main cause in most reports. Rheumatic heart disease follows these in frequency, and syphilis is the fourth important cause. Other factors are present in only a small number of cases. It is apparent that statistics on the incidence and etiology of heart disease must be classified on a better basis. The most representative statistics are those based on large general hospital admissions. In spite of the low value generally conceded to vital statistics and the high value placed on autopsy figures, the percentage of recorded heart disease is approximately the same. Vital statistics place the percentage of deaths due to organic heart disease at 20%. Autopsy figures from four large general hospitals give an average of 18%.

Summary. 1. The incidence of organic heart disease at the Cook County Hospital for the 18-month period, from January 1, 1932, to June 30, 1933, was 1.7% of the total hospital admissions and 7.2% of the medical admissions.

2. Of the 1646 patients, 38% died in the hospital during the stated period; this was 6.7% of the hospital deaths and 14.4% of the medical deaths.

3. In this study the common age for heart disease was the 40-to-60-year period; it occurred most frequently in the 6th decade in the white patients and in the 5th decade in the colored patients.

4. Hypertension was the most common cause of organic heart disease regardless of the race or sex.

5. Arteriosclerotic and rheumatic heart disease were more common in the white patients.

6. Syphilitic and hypertensive heart disease were more common in the colored patients.

7. Arteriosclerotic heart disease was 5 times more common in the white patients.

8. Pulmonary emphysema as a cause of myocardial insufficiency was practically confined to white males.

9. Rheumatic heart disease was twice as frequent in the white patients.

10. Syphilitic heart disease was 4 times as frequent in the colored patients.

11. Hypertensive, arteriosclerotic, rheumatic and syphilitic heart disease accounted for 90% of the cases of organic heart disease.

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A STANDARDIZED EXERCISE TOLERANCE TEST FOR PATIENTS WITH ANGINA PECTORIS ON EXERTION.*

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Although our knowledge of angina pectoris has increased considerably since its first description by Heberden,[1] the diagnosis still rests entirely upon a careful evaluation of the patient's own description of his subjective sensations. We have at our disposal few or no objective criteria with which to confirm the diagnosis: physical examination and Roentgen ray of the heart may reveal nothing of diagnostic importance; the electrocardiogram may be perfectly normal in some cases, while in other instances trivial variations may be of unrecognized significance.[2] Although the typical symptom complex is easily recognized, there are variations which are important, taxing the judgment of the most able clinicians. It is not surprising, therefore, that patients with angina pectoris are often incorrectly treated for peptic ulcer, neuritis or other diseases,

* This study was aided by a grant from the William W. Wellington Memorial Research Fund of the Harvard Medical School. It is the thirteenth study of the treatment of patients with congestive heart failure and angina pectoris by total ablation of the thyroid.

or that many patients supposedly suffering from angina pectoris really have no organic heart disease.

In addition to the pitfalls in diagnosis, there are difficulties in estimating accurately the severity of the disease, in evaluating the progress of the condition and the results of therapy. These difficulties arise from the variability of the condition under which attacks are precipitated in daily life, their irregularity in frequency, the effect of suggestion, the subconscious self-imposed limitation in activity and the necessity of relying entirely on the patient's impression. In many individuals temporary improvement occurs during the warm months and may be interpreted erroneously as the result of therapy.

Because observation of the patient during an attack would be helpful in diagnosis, certain methods of precipitating anginal attacks have been proposed during recent years. The subcutaneous injection of epinephrin[3] is not without danger[4] and may produce anginal attacks in patients not afflicted with this condition.[5] The precipitation of attacks by the production of anoxemia[6] is undoubtedly of diagnostic value. Neither method produces anginal attacks under conditions which have a close clinical counterpart, nor do they permit accurate evaluation of the severity of the spontaneous attacks or of the ease with which they are precipitated in daily life. Wayne and La Place[7] have recently reported studies on angina pectoris of effort, thus utilizing a physiological stimulus which normally causes anginal attacks.

Early in 1933, in connection with the treatment of patients with angina pectoris by total ablation of the thyroid gland, we were confronted with the necessity of confirming the diagnosis of angina pectoris, of determining the severity of the symptoms and of evaluating the benefits of this therapeutic measures.[8] A simple and safe method was sought for the production of anginal attacks under conditions comparable to those producing attacks in daily life. Such a method to be of value in diagnosis should precipitate angina pectoris in the vast majority if not all patients with this condition, but should not cause attacks in patients not suffering from this disease. To be of help in the evaluation of therapy, the method should give objective evidence of the patient's condition and should yield substantially the same results on repetition.

Although attacks of angina pectoris may occur when the patient is at rest or even asleep, the majority of patients develop angina on exertion or emotion. The influence of the mental state of the individual is of undoubted importance, but this factor is difficult to measure or reproduce. The amount of exercise which precipitates an attack in a given individual appears to vary considerably from time to time; but the clinical histories of these patients suggest several possible causes for these variations. These include type and rate of exercise, temperature of the environment, excitement,

food, medication, recent attacks of angina and recent exertion. We have studied the influence of each of these factors, and on the basis of these studies have evolved a method for the production of anginal attacks which seems to fulfill the requirements outlined above. This method has been in use for over a year and has given satisfactory results. Our first experience with the test has been reported.[8] The purpose of this communication is to describe the method in detail and to report the results of our studies to date.

Factors Which Influence the Patient's Exercise Tolerance. *Type of Exercise.* The type of exercise used in an exercise tolerance test should be one with which the patient is familiar and which requires little or no training. The bicycle ergometer in our hands has given quite variable results presumably because the ordinary hospital patient is not accustomed to this type of exercise and, therefore, requires considerable training and practice before he can perform the work satisfactorily. This is especially true of patients in the age group in which angina pectoris is most frequent.

TABLE 1.—THE AMOUNT OF WORK NECESSARY TO PRODUCE ANGINA PECTORIS ON THE TWO-STEP STAIRCASE COMPARED WITH THE AMOUNT NECESSARY WHEN EXERCISING ON ORDINARY FLIGHTS OF STAIRS.

Case No.	Weight, pounds.	Two-step staircase (each trip 18 inches high).			Ordinary staircase (each flight 20 to 22 steps, each step 7½ inches high).			
		Temp. °F.	Amount of work.		Temp. °F.	Amount of work.		
			Trips.	Foot pounds.		Flights.	Steps.	Foot pounds.
3* . .	173	53–56	12–13	3,100– 3,400	63–69	2.8	61	6,250
5* . .	156	52–58	18–24	4,200– 5,600	77	1.8	37	3,400
6* . .	147	58	18–22	3,950– 4,850	78	1.9	41	3,600
9 . .	110	51–54	22–26	3,650– 4,300	40–60	7.0	152	10,000
23 . .	146	46–51	38	8350	48–64	4.9	103	8,900
26 . .	165	48–58	36–45	8,900–11,200	52–54	5.7	124	12,100
21 . .	169	52–58	34–38	8,650– 9,650	72	9	184†	18,400
29 . .	143	50–56	58–66	12,500–14,200	72	9	184†	15,700

* In these individuals variation in temperature of the environment caused no great difference in the amount of work necessary to produce angina pectoris.

† No attack of angina pectoris was produced.

The ordinary staircase is unsuitable for exercise tolerance tests for several reasons. Exercise on a long staircase may precipitate severe angina when the patient is half way up the flight, and so he may be temporarily unable to go up or down and be forced to rest on the staircase. Variations in the height of the steps, the length of the flights of stairs and the size of the landings prevent comparing the results obtained in different buildings. Furthermore, the number of stairs required (often 4 or more flights, Table 1) is not available in all buildings. Finally, the temperature of a stair-

well is difficult to regulate, especially during the summer months and, as will be shown, the temperature of the environment in which the exercise is performed greatly influences the amount of exercise necessary to product an attack of angina.

In order to overcome these objections we have used a two-step staircase similar to that described by Master and Oppenheimer[9] (Fig. 1). The exercise of walking up and down steps is familiar to the patient and requires no training. The amount of exercise can be varied readily. When the patient develops an attack of angina, he can rest safely in the very room in which the exercise is performed. Being portable, the staircase can be moved readily to a room with regulated temperature. The number of foot pounds of work performed may be estimated roughly by multiplying the patient's weight by the height of the staircase ($1\frac{1}{2}$ feet) and the number of trips performed. This is inexact, however, for it ignores the work done in descent of the staircase.

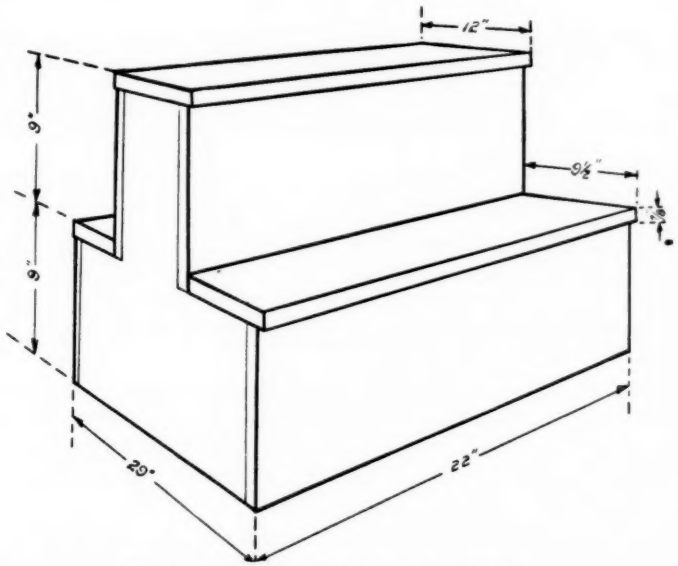

FIG. 1.—Dimensions of the two-step staircase.

We have found that the majority of patients suffering from angina pectoris develop typical attacks when exercising on the two-step staircase under standard conditions. When the test is repeated, the same amount of exercise invariably precipitates an attack in the same individual, providing the standardized conditions are reproduced.

Rate of Exercise. To obviate the necessity for training and to minimize the effect of excitement the patient is allowed to choose

his own rate. The average speed of exercise for all patients was 13 trips per minute.* Only an occasional patient exercised at a rate substantially different. The rate for each individual was reasonably constant even when the test was performed at widely separated intervals of time (Table 2). Doubtless, exercise at much slower or faster rates would give different results.

TABLE 2.—COMPARISON OF THE RESULTS OF THE STANDARDIZED EXERCISE TOLERANCE TEST WHEN REPEATED AFTER AN INTERVAL OF 2 OR MORE MONTHS.

Case. No.	Date.	Temp. of room, °F.	Duration of exercise, min.	Amount of exercise, trips.	Rate of exercise, trips per min.
13	4/ 3/33	56	1.5	22	14½
	6/ 2/33	51	1.5	22	14½
4	5/ 5/33	48	1.3	15	12
	7/ 5/33	56	1.2	13	11
30	10/27/33	53	4.9	63	13
	12/22/33	53	5.3	70	13
10	10/27/33	53	2.0	20	10
	1/ 2/34	50	1.9	19	10
11	10/25/33	50	1.8	20	11
	1/11/34	54	2.0	19	9½
2	5/15/33	54	1.3	12	9½
	9/18/33	56	0.5	6	12
21	4/17/33	58	3.0	38	12½
	11/25/33	52	2.8	36	13
24	4/17/33	58	2.7	40	15
	12/22/33	50	3.7	59	16

Excitement. Exercise on the two-step staircase is so similar to acts performed in daily life that the emotional factor is minimized. In 7 out of 30 individuals, however, we found that at the time of the first test angina was developed after considerably less exertion than at subsequent tests (Table 6). This discrepancy was due presumably to excitement and existed only at the time of the first test.

Temperature. The increased frequency of anginal attacks during the cold winter months is well recognized. Measurement of the amount of work that an individual can perform in warm and cold atmospheres is presented in Table 3. Because of convenience, a Barach oxygen chamber was used in most experiments. The chamber was filled with ordinary air and the temperature was maintained roughly between 45° and 55° F. A large refrigerator, of the type available in most hospitals and markets, was used in several tests. The results obtained in the oxygen room and in the refrigerator were identical.

The temperature used did not cause shivering and was not uncomfortable for the patients even when dressed in thin hospital attire. Our patients usually began to exercise within 5 minutes after entering the cold room. More prolonged exposure did not affect the results. None developed angina at rest in the cold room.

* The term "trip," as used here signifies one ascent and one descent of the staircase.

Five of 15 patients showed striking differences in the amount of exercise necessary to precipitate angina at different temperatures (Table 3). Two (Cases 26 and 29) did not develop attacks at room temperatures even though they exercised to the point of exhaustion. Two others (Cases 21 and 27) showed extremely variable results when exercising at room temperatures. Two of these 4 patients (Cases 21 and 29) climbed 9 flights of stairs (average temperature, 72° F.) without angina. The fifth individual (Case 17) developed marked palpitation at room temperature, which prevented continuing the exercise to the point of angina. Each of these 5 patients invariably developed typical attacks of angina pectoris after relatively small amounts of exercise in the cold room.

TABLE 3.—THE EFFECT OF TEMPERATURE ON THE AMOUNT OF EXERCISE NECESSARY TO PRODUCE ANGINA PECTORIS.

Case No.	Temp. of room, °F.	Amount of exercise, trips.	Anginal attacks.
1	49–51	9–11	Present.
	62–64	9–11	Present.
3	53–56	12–13	Present.
	77–83	15–17	Present.
4	48–57	13–15	Present.
	79	18	Present.
5	52–58	15–24	Present.
	73–77	20–24	Present.
6	58	18–22	Present.
	74–76	16–19	Present.
8	48–56	13–21	Present.
	75–76	13–21	Present.
13	50–56	22–26	Present.
	77	24	Present.
14	46–48	26–29	Present.
	82	37	Present.
16	48–56	24–37	Present.
	79–81	30–32	Present.
27	43–48	53–57	Present.
	76–78	44–78	Present.
28	48–56	58–66	Present.
	79	65	Present.
21*	52–58	34–38	Present.
	75	39	Present.
	80	76	Questionable.
	76	100	No attack.
26	48–58	36–45	Present.
	81	40	No attack.
	76	56	No attack.
29*	50–56	58–66	Present.
	78	100	No attack.
	78	229	No attack.
17	46–50	29–30	Present.
	75–76	13–21	Severe palpitation preventing further exercise; no attack.

* These patients were able to climb 9 flights of stairs (184 steps, each 7¼ inches high) at 72° F. without developing angina pectoris.

Effect of Meals. Patients frequently develop angina more readily after a heavy meal. Our standard tests have been performed either in the fasting state or at least 1 hour after a light meal. Under such conditions no important variations in the amount of exercise required to produce attacks were evident. Three patients were tested 20 minutes after a heavy meal. In 2 of these individuals the meal did not influence the amount of work necessary to precipitate an attack, whereas the third patient developed an attack after performing only about two-thirds of his usual amount of work (Table 4).

TABLE 4.—THE EFFECT OF FOOD ON THE NUMBER OF TRIPS NECESSARY TO PRODUCE ANGINA PECTORIS.

Case No.	Fasting, trips.	1 hr. or more after light meal, trips.	20 min. after heavy meal, trips.
8	15	17–21	13
16	27	24–37	25
28	66	58–64	42

TABLE 5.—COMPARISON OF THE AMOUNT OF WORK REQUIRED TO PRODUCE ANGINA PECTORIS UNDER STANDARDIZED CONDITIONS AND WHEN THE TEST WAS AGAIN PERFORMED AFTER 5 TO 10 MINUTES' REST.

Case No	Standardized test, trips.		
	1st test.	2d test.	3d test.
2	12	8	
4	13	20	
13	25	40	
19	35	46	
29	65	147	
	66	154	98*
	58	150	85†
28	64	8	

* On hour after the preceding anginal attack.
† Four hours after the preceding anginal attack.

Effect of Medication. After taking nitroglycerin patients were often able to perform more exercise before developing an attack. For example, one of our patients (Case 30) who regularly developed angina after 63 to 70 trips was able to perform 100 trips 1 hour after taking a $\frac{1}{100}$-grain nitroglycerin pill.

Effect of Recent Attacks of Angina Pectoris. Many patients develop an attack shortly after going out into the cold, but thereafter may be able to exercise outdoors for hours without experiencing pain. Others find that the first attack predisposes them to subsequent attacks, while still others find that their tolerance for exercise is approximately the same at all times. Similarly, previous exercise or preceding attacks of angina pectoris affected the results of our tests. In 6 patients an attack of angina was precipitated, and after 5 to 10 minutes' rest the test was repeated (Table 5). In 2 of these (Cases 2 and 4) the results of the second test were not significantly different from the first. Three others (Cases 13, 19, 29) were able to do more work than was possible at any

other time. This was especially striking in one patient (Case 29) who was able to do between 2 and 3 times as much work as usual after he had experienced the first attack. This protective effect

TABLE 6.—THE AMOUNT OF EXERCISE REQUIRED TO PRECIPITATE ANGINA PECTORIS IN 34 PATIENTS.*

Case No.	Date of test, 1933 and 1934.	Temperature of room, °F.	Duration of exercise, min.	Amount of exercise, trips.
1 ..	6/20	51	1.2	9
	6/21	49	0.8	11
2 ..	5/15	54	1.3	12
	5/18	46	0.5	6
3 ..	10/27	53	1.0	12
	11/10	56	1.0	13
4 ..	5/ 1	54	...	6
	5/ 5	48	1.3	15
	7/ 3	57	1.2	13
	7/ 5	56	1.2	13
5 ..	11/10	58	1.2	15
	11/20	58	2.2	24
	11/27	52	1.4	18
6 ..	11/10	58	1.8	22
	11/20	58	1.5	18
7 ..	11/27	52	1.2	16
	11/28	56	1.6	21
	11/29	55	1.8	23
8 ..	11/15	55	2.2	18
	11/16	50	2.1	21
	11/17	48	1.5	17
	11/20	56	1.2	15
	11/21	55	1.2	13
9 ..	12/ 1	51	1.1	22
	12/26	51	1.2	23
	1/11	54	1.0	26
10 ..	10/27	53	2.0	20
	12/22	52	1.7	17
	1/ 2	50	1.8	19
11 ..	10/23	50	2.4	25
	10/25	46	1.8	20
	1/11	54	2.0	19
12 ..	7/17	55	2.0	21
	7/18	58	2.3	21
13 ..	4/ 3	56	1.3	22
	4/29	53	1.7	22
	4/30	53	2.2	25
	5/ 1	51	1.8	26
	6/19	50	1.5	22
14 ..	10/23	50	0.8	8
	10/28	46	2.1	26
	11/ 2	48	2.1	29
	11/ 3	48	2.1	26
15 ..	10/27	53	1.3	22
	11/20	58	2.3	34
16 ..	11/15	55	1.9	24
	11/16	50	2.5	29
	11/17	51	3.0	37
	11/18	48	2.3	27
	11/21	56	1.8	25
17 ..	9/26	47	2.6	30
	9/27	46	2.3	29
	9/28	50	2.4	29
18 ..	7/14	55	1.9	28
	7/17	58	1.5	24
	7/18	58	1.8	32
	7/19	60	1.8	32
19 ..	11/ 6	44	1.5	19
	11/ 8	49	2.3	35
	11/20	56	3.5	31
20 ..	12/28	53	1.9	36
	1/ 2	48	2.4	32
	1/ 4	48	2.5	36
21 ..	4/17	58	3.0	38
	11/ 4	52	2.0	34
	11/25	52	2.8	36
22 ..	10/23	50	2.6	37
	10/28	55	4.0	47
23 ..	12/11	46	3.4	38
	12/26	51	3.1	38
24 ..	4/17	58	2.7	40
	12/22	50	3.5	59
25 ..	10/27	53	2.7	30
	10/30	47	5.4	44
	12/30	52	5.5	56
	1/13	45	4.0	50
26 ..	11/10	58	4.0	40
	11/24	52	3.7	36
	1/ 2	48	3.9	45
27 ..	10/ 4	46	2.8	39
	10/ 5	43	4.2	57
	10/ 7	48	3.8	53
	10/ 9	45	3.9	56
28 ..	11/16	50	2.9	58
	11/17	48	2.9	64
	11/20	56	3.3	66
29 ..	3/ 2	56	4.4	65
	3/12	50	4.3	66
	3/13	50	3.8	58
30 ..	10/27	53	4.9	63
	12/22	53	5.3	70
31 ..	10/23	50	0.5	1
32 ..	11/10	48	3.8	33
33 ..	11/10	58	3.8	33
34 ..	10/26	49	2.6	34

* There were 27 males and 7 females, with ages varying from 41 to 72.

apparently lasted for several hours. In this individual severe exercise even without the development of an attack apparently had some protective effect. The sixth patient (Case 28) found that on repetition of the test he was able to do only about one-eighth as much work as he usually could accomplish.

A Standardized Exercise Tolerance Test. With a knowledge of the physiologic conditions which cause variations in the amount of exercise necessary to produce an attack of angina pectoris, it is possible to standardize these conditions so that the amount of exercise necessary to produce an attack serves as an index of the severity of the patient's illness. Reproduction of these standardized conditions enables one to test the patient under identical conditions regardless of season or climate, and makes it possible to evaluate the results of therapy. This is the basis of the standardized exercise tolerance test used at the Beth Israel Hospital during the past year. These standardized conditions reproduce the environmental situation which gives rise to angina pectoris in daily life and so permit personal observation of the clinical signs and symptoms under controlled conditions.

Method. The test is performed in a room, the temperature of which is adjusted to between 45° and 55° F. The patient is tested at least 1 hour after a light meal or before breakfast on a day during which he has not experienced an anginal attack. The results are compared with single tests on other days. In patients who have several attacks during the day, it may be necessary to perform the test despite recent angina. In such individuals, repetition of the test at several subsequent dates will reveal whether or not constant results can be obtained under such conditions.

The exercise consists in repeatedly walking up and down the two-step staircase described above (Fig. 1), at a rate which is usual or comfortable for the patient. Dizziness is avoided by having the patient turn toward the same wall at the completion of each trip on the staircase.

The patient continues the exercise until he develops an attack of angina pectoris severe enough to cause him to stop. The number of times the patient mounts the staircase, that is to say, the number of trips performed, is recorded with a tally counter. The rate and the duration of the exercise are measured with a stopwatch.

Results. During the past year over 500 attacks have been studied in 57 consecutive patients, diagnosed as suffering from angina pectoris. Each of the individuals had been studied previously either in the Out-Patient Department or on the medical wards of the Beth Israel Hospital. The diagnoses had been made by various members of the hospital staff and had been based entirely on the clinical findings. In 4 of these patients it was impossible to perform the test because of infirmity or lack of coöperation. The remaining 53 individuals were able to exercise without difficulty, even though many had been restricted in activity for years.

Analysis of Positive Results. Exercise under the standard conditions precipitated attacks of angina pectoris in 34 individuals (7 women and 27 men, Table 6). The amount of exercise necessary

to produce an attack varied in the different individuals. In most instances (22 cases), 20 to 40 trips were necessary. The sequence of events during exercise was uniform. After a certain amount of exercise the patient began to experience discomfort, which was not intense and did not interfere with continuation of the exercise. Frequently, at this time, the patient's expression became anxious and occasionally one hand reached involuntarily toward the sternum. Within 2 to 10 trips after the onset of these symptoms, the discomfort increased rapidly, and suddenly became so intense that the patient was forced to stop. This point was quite definite and was taken as the end point of the test.

The patients always stated that the attacks produced were identical with those experienced in daily life. Observation and questioning of the patient at the time of the attack frequently brought to light details which were unobtainable in the usual clinical history. The distribution and character of the pain could be determined definitely and accurately. The duration of the attack could be measured.

There have been absolutely no untoward effects from the exercise or the induced attacks. Dyspnea was usually quite marked at the onset of the attack, but cyanosis, pallor or flushing were not observed. In a few individuals the pain increased in severity after the exercise had been stopped. These were the only persons who required nitroglycerin to secure relief from the attack. Some individuals experienced headache rather than relief of chest pain after nitroglycerin. In these persons, the attacks were of short duration ($\frac{1}{2}$ to $1\frac{1}{2}$ minutes) and presumably subsided before the nitroglycerin had begun to act, so that only the unpleasant effects of the drug were experienced.

The sudden development of pain, severe enough to cause the patient to stop, the motionless attitude of the patient during the attack, the anxious expression with hands pressed to the sternum and the prompt relief by nitroglycerin when administered gave objective evidence sufficient to establish the diagnosis of angina pectoris in the majority of patients. In other individuals careful questioning during or immediately after the attack was of great aid in establishing the diagnosis. It is hardly conceivable that patients not subject to attacks of angina pectoris should develop such symptoms under the physiologic conditions of this test.

The number of trips necessary to precipitate an attack of angina pectoris gave insight into the frequency of attacks in daily life and indicated the severity of the patient's illness. The intensity of the individual attack varied, however, in different individuals and was not related to the number of trips necessary to induce an attack.

Constancy of Results. In 30 instances the standardized test was repeated one or more times on different days (Tables 2 and 6). The amount of exercise necessary to precipitate an attack of angina was

quite constant for each individual, even though the tests were separated from each other by several months (Table 2). In the analysis of the data the result of the first test was eliminated when it differed markedly from the results of subsequent tests, for, as has been demonstrated above, angina is frequently precipitated more readily at the time of the first test. Of the 30 cases retested, 20 showed a maximum variation of 6 trips in the amount of exercise necessary to precipitate angina pectoris. Four of the remaining 10 cases showed a maximum variation of less than 10 trips, 2 showed checks within 12 trips and the remaining 4 had only 2 tests.

Analysis of Negative Results. Of the 53 patients who performed the test, 19 did not develop angina pectoris when exercising under standard conditions. These patients illustrate the difficulties and dangers in making a diagnosis of angina pectoris on the basis of history alone.

GROUP I. *Patients Who Were Shown to Have No Angina Pectoris.* Six patients developed symptoms on exertion which were identical with those for which they sought medical advice. Observation of these patients during the time that the symptoms persisted enabled us to evaluate their symptomatology more carefully than was previously possible. Four of these patients complained of substernal "choking" on exertion. This was demonstrated to be dyspnea, due to emphysema. This dyspnea gradually developed and gradually increased during the exercise, and subsided slowly thereafter with no precordial element and no radiation. A fifth patient developed sharp sticking pains in the left midaxillary line which persisted less than 1 second and which did not prevent him from continuing the exercise to the point of exhaustion. In the sixth case it was demonstrated that the pain was not related to exertion and was present only when pressure was exerted on the 6th and 7th ribs in the axillary line.

GROUP II. *Patients Who Had Had No Recent Attacks of Angina Pectoris.* Three patients who had clearly defined histories of angina pectoris had not experienced attacks for many months. In none of these individuals were we able to precipitate angina by the exercise tolerance test. One of these individuals had noticed the disappearance of anginal pain following coronary occlusion 2 years previously. Another patient had had 2 attacks of constricting chest pain about 1 year before the test was performed, but since that time he had been entirely free from pain despite the fact that his occupation (peddler) necessitated climbing many flights of stairs every day. The third patient experienced no anginal pain, either spontaneously or induced, during 4 months of observation.

GROUP III. *Patients in Whom the Diagnosis of Angina Pectoris Was Doubtful.* In 9 patients, reëvaluation of the case history by independent observers failed to corroborate the diagnosis of angina pectoris. In these patients, the description of the attacks was found

to be atypical. Because of the uncertainty of the diagnosis, 4 cases were admitted to the hospital wards. In these individuals exercise in the cold room and out of doors in cold, windy weather repeatedly failed to precipitate angina. Subcutaneous injections of epinephrin in increasing doses up to 1 cc. of a 1 to 1000 solution failed to precipitate anginal attacks in 3. The fourth patient developed an attack of angina with 1 cc., but not with smaller doses. This patient, on further study, repeatedly revealed concentrations of over 200 mg. of protein in the lumbar spinal fluid and normal concentrations of protein in the cisternal fluid, which suggested that his complaints were due to disease of the central nervous system. The remaining 4 patients were able to exercise to the point of fatigue without developing angina. All 9 patients in this group have been followed for periods varying from 3 to 9 months, without having developed any further evidence of angina pectoris.

GROUP IV. *Patients Who Had Angina But in Whom the Diagnosis Could Not Be Confirmed by the Exercise Tolerance Test.* One patient with hyperthyroidism had developed the typical symptom complex of angina pectoris with the onset of his thyrotoxicosis. Despite a clinical history of angina on both rest and effort, we were unable to precipitate pain by prolonged exertion.

Comment. The standardized exercise tolerance test offers a simple and safe method of precipitating attacks of angina pectoris under controlled conditions duplicating those under which attacks are produced in daily life. The physiological conditions, such as temperature, excitement, food, medication and the influence of recent attacks, which were found to modify the amount of exercise necessary to precipitate angina, have their counterpart in daily life, and are probably in part responsible for the variable histories which these patients give. Further studies may reveal other factors of importance. The relative constancy of the amount of work necessary to produce an attack of angina under standard conditions indicates some fundamental relationship between the amount of work done, the demands upon the heart and the ability of the heart or coronary vessels to meet these demands.

The ability to produce attacks of angina pectoris at will affords a means of diagnosis, evaluation of therapeutics and study of the basic physiology of this condition. The influence of environmental factors has been presented above. The therapeutic benefits of medication and further reports on the effect of total ablation of the thyroid gland will be the subjects of forthcoming communications. Studies are also being carried out on the changes in blood pressure, heart rate, velocity of blood flow, minute volume output of the heart, respiration and oxygen consumption of the body during anginal attacks.

The opportunity to observe the patient during an attack may be

of great aid in establishing the diagnosis. Cases 7 and 28 had been treated for gastro-intestinal disorders for several years. It was possible to demonstrate that the epigastric discomfort of which these patients complained was a clutching sensation which came on only with exertion and radiated in one case to the suprasternal notch and in the other case to the manubrium and down the left arm. Case 23 had been treated for neuritis of the left arm for over a year. Personal observation of this patient during attacks demonstrated that this pain came on with exertion, began in the left wrist and radiated up the inner aspect of the left arm to the substernal region. In several patients whose clinical histories were difficult to evaluate because of language difficulties, the invariable onset of pain with specific amounts of exercise and the radiation typical of angina pectoris established the diagnosis.

Mackenzie[10] has pointed out the difficulties in obtaining a clear description of the intensity and distribution of pain referred from the heart. Observation of the patient while the pain is present may make it possible to obtain an accurate conception of the severity of the discomfort and may enable the observer to outline accurately the distribution and limits of the pain.

The factors precipitating angina pectoris are varied, and because of this, the ability to precipitate angina under the standard conditions of the test cannot be considered pathognomonic of the condition. Attacks of angina may be precipitated not only by exertion but also by emotion, paroxysmal heart action, adrenalin or anoxemia. Attacks may also occur when the patient is at rest or even during sleep. Most patients, however, develop attacks of angina on exertion, even those who also have attacks on excitement or when at rest. The fact that the clinical characteristics of the attacks are identical under a variety of conditions suggests a common underlying mechanism. The study of angina pectoris under the conditions outlined above is of advantage in that the predisposition of the patient to anginal attacks can be measured accurately, and the attacks provoked and studied at will. The inability to induce an attack under conditions duplicating those which cause attacks in daily life, while not proof positive of the absence of this disease, must leave the diagnosis open to question and should lead the examiner to reëvaluate the history carefully. Another more probable basis for the symptoms usually will be found. One of our patients undoubtedly had a compensation neurosis. Two others had sharp sticking pains in the region of the apex, which were not related to exertion and which were probably functional in nature. Reference has already been made to the difficulty in properly evaluating the symptom of "choking," of which many patients with pulmonary disease and early congestive failure complain. The differentiation between the heart pain of congestive

heart disease and true angina pectoris frequently offers difficulties which may be eliminated by the exercise tolerance test.

The relative amount of work required to precipitate attacks of angina pectoris in an individual gives us a means of evaluating the severity of the condition. Thus, Case 29 who could perform approximately 65 trips before angina developed was obviously less seriously incapacitated than Case 1 who could perform only 9 to 11 trips. Finally, the relative constancy of the amount of work required under standardized conditions to precipitate attacks in the individual patient enables one to evaluate the patient's condition from time to time regardless of season or climate and offers an objective criterion for evaluating the effect of therapy.

Summary. 1. A simple and safe standardized exercise tolerance test is described for use in patients with angina pectoris.

2. The results of the test in a group of 57 consecutive patients with the clinical diagnosis of angina pectoris are presented.

3. Exercise performed under the standard conditions of the test induced attacks in 34 patients. These attacks were precisely like those experienced in daily life.

4. When the standardized test was repeated, even months later, the same amount of exercise again precipitated an attack in the same individual.

5. Nineteen patients did not develop an attack under the standardized conditions. The diagnosis of angina pectoris eventually proved to be exceedingly doubtful in all but one of these patients.

6. Objective evidence is presented illustrating the influence of various environmental factors on the amount of exercise necessary to precipitate attacks of angina pectoris in patients with this condition.

7. The test affords a means of investigating angina pectoris and is of distinct value as an aid in diagnosing doubtful cases and in evaluating both the condition of the patient and the results of therapy.

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WHAT TREATMENT IN EARLY SYPHILIS ACCOMPLISHES.†

I. RELAPSE AND "CURATIVE" RESULTS.

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FROM any material on early syphilis it is highly desirable to secure a forward-looking glimpse into the ultimate outcome of treatment for syphilis as it concerns the individual patient. The previous studies of early syphilis[1] have indicated certain landmarks of procedure and have quite clearly demonstrated the agents and methods for the control of infectiousness. The difficulties of follow-up in clinic patients and the time required to collect so large a material, as has been pointed out, rapidly reduce the mass of material available for study with each month and year elapsed since the onset of the infection. Of the original 6807 cases with diagnosed early syphilis on admission, there remain 1360 patients who were under treatment or observation for 2 years or longer; 5 to 10 years after infection there remain only 295 cases on whom even an approximation to ultimate outcomes can be discussed; and of cases observed for 15 years, a mere thimbleful of 14 cases. The discussion here presented, then, cannot be accepted as that of true end results of modern treatment. Rather it is a sampling for trends in the effort to see what, if anything, we are accomplishing and whether or not it is worth while. Moreover, it is necessary to realize that the 1360 cases forming the material of this study have not been on a 2-year probationary period since the cessation of treatment. Treatment in many cases has been continued through a part or all of the 2-year period. Had the study been restricted to patients who had had 2 years' probation following the cessation of all treatment, the material would through shrinkage have lost much of its statistical usefulness.

The purpose of this study, then, is to analyze the course of treated early syphilis through a period of 2 years or longer, as distinguished from the larger previously studied group, observed for only 6 months or longer. It is hoped that such a study will begin to indicate in what ways and to what degree treatment is worth while for the

* Names with asterisk represent the U. S. Public Health Service; names without asterisk represent the Coöperative Clinical Group.

† This and the two following studies were conducted by the coöperation of the syphilis clinics of the University of Pennsylvania, Western Reserve University, the Johns Hopkins University, The Mayo Clinic, the University of Michigan, assisted by the U. S. Public Health Service and supported by a special fund contributed by an anonymous donor and a grant by the Milbank Memorial Fund.

individual patient; and whether, with a given period and amount of treatment, something approaching a standard result can be obtained. Such a definition of outcome and procedure would enable the physician to speak in much more definite terms to himself and to his patient. It would reduce, and subsequent studies might ultimately do away with, the always present uncertainty as to when to stop; and if no endpoint could be determined, a comparison of the outcome of treated and untreated cases might furnish a basis for demonstrating the worthwhileness or the relative futility of modern treatment as regards the individual outcome. (See subsequent paper.) Insofar as the material in early syphilis permits, such comparisons have been made. Inevitably the tone of such a presentation will be more speculative than the preceding studies on early syphilis by the Coöperative Clinical Group; for in the last analysis, we are not dealing with time periods which permit of assertion, or with material so controlled that speculation can be eliminated. Judicious theorization may none the less serve the purposes of constructive future observation and thought.

This paper will also include, by way of catching up certain loose threads in previous studies, a survey of the total early syphilis material of 6807 cases from the standpoint of all types of relapse. This will meet the objection that previous estimates of relapse were based on a 6 months' material in which a very considerable proportion of patients had presumably entered and passed through the period of greatest frequency of relapse and dropped from observation before they could be included in the 6 months' observation series.

In order to determine whether the 2-year observation material and the conclusions derived from it can be regarded as fairly representative of what may be expected of early syphilis as a whole, as influenced by the stage of infection on beginning treatment, the proportions of seronegative and seropositive primary, early secondary and delayed secondary syphilis in the total cases diagnosed as early syphilis were compared with the proportions in the 2-year observation group. The practical identity of the proportions in the two groups indicates that the 2-year cases are a fair sample of the whole group of early syphilis, and that expectancy and results based on the 2-year group may properly be regarded as applicable to early syphilis in its entirety, if the early syphilis patient will persist in treatment and observation for 2 or more years.

Cases of Early Syphilis Under Observation-Treatment for any Period of Time. *Frequency of All Forms of Relapse.* In Table 1, all forms of relapse are considered in terms of the stage of the disease at which the patient began treatment. The total incidence of relapse, 10.1%, is lower than in the cases observed for 6 months or longer (19.7%). The explanation for the disparity lies in the fact that nearly half the material included in the total diagnosed

was observed so short a time that no opportunity to observe the maximum incidence of relapse was provided. The figures in previous studies, therefore, better represent the incidence of early relapse.

TABLE 1.—COMPARATIVE INCIDENCE OF RELAPSE IN PATIENTS WITH EARLY SYPHILIS TREATED OR OBSERVED FOR 6 MONTHS OR LONGER WITH THOSE FOR ANY PERIOD OF TIME.

Type of relapse.	Seronegative primary.		Seropositive primary.		Early secondary.		Delayed secondary.		Total.	
	Total cases treated.	Six months or more.	Total cases treated.	Six months or more.	Total cases treated.	Six months or more.	Total cases treated.	Six months or more.	Total cases treated.	Six months or more.
					Number.					
Early infectious:										
Mucocutaneous	59	56	125	118	220	214	7	6	411	394
Ocular	2	2	12	11	32	28	..	..	46	41
Central nervous system:										
Symptomatic	10	9	35	33	103	89	1	1	149	132
Asymptomatic	13	12	20	13	83	77	8	8	124	110
Benign, late	3	3	10	10	36	36	1	1	50	50
Cardiovascular	3	3	3	3	24	24	..	..	30	30
Visceral	..	..	..	..	2	2	..	..	2	2
Total cases relapsing*	78	74	176	159	417	392	16	15	688	640
Total cases	709	342	1319	585	4640	2252	139	65	6807	3244
					Per cent.					
Early infectious:										
Mucocutaneous	8.3	16.4	9.5	20.2	4.7	9.5	5.0	9.2	6.0	12.1
Ocular	0.3	0.6	0.9	1.9	0.7	1.2	..	..	0.7	1.3
Central nervous system:										
Symptomatic	1.4	2.6	2.7	5.6	2.2	4.0	0.7	1.5	2.2	4.1
Asymptomatic	1.8	3.5	1.5	2.2	1.8	3.4	5.8	12.3	1.8	3.4
Benign, late	0.4	0.9	0.8	1.7	0.8	1.6	0.7	1.5	0.7	1.5
Cardiovascular	0.4	0.9	0.2	0.5	0.5	1.1	..	..	0.4	0.9
Visceral	..	..	..	..	0.04	0.09	..	..	0.03	0.06
Total cases relapsing	11.0	21.6	13.3	27.2	9.0	17.4	11.5	23.1	10.1	19.7

* Each relapse is recorded, although some cases have 2 or more.

As regards the individual forms of relapse, the comparative figures are: Mucocutaneous, total diagnosed group, 6%; 6 months' observation group, 12.1%; asymptomatic neurosyphilis, 1.8% *vs.* 3.4%; symptomatic neurosyphilis, 2.2% *vs.* 4.1%; cardiovascular, 0.4 *vs.* 0.9%.

The patient who begins treatment in the seropositive primary stage of syphilis has the highest incidence of mucocutaneous relapse. Why is this so? Because he has had to combat an already intrenched (Wassermann positive) infection, with no other aid than

that of treatment, lacking the immunizing or protective effect of his general secondary reaction. The patient with seronegative primary syphilis finds himself with an unintrenched infection, compelled to rely entirely on the effect of treatment. He achieves an advantage by the "unintrenchment," a disadvantage in the form of increased frequency of mucocutaneous relapse by the lack of systemic reaction, which brings him out midway between the patient with seropositive primary syphilis and the patient who has had florid secondaries. Thus it appears that so far as mucocucutaneous relapse is concerned, the most vulnerable position a patient can hold is that of a seropositive primary case. His skin and mucous membranes will, so to speak, be inspired to, but will not achieve full protective reaction. He will have a tendency, an exaggerated tendency, to relapse.

If such a group of considerations could be found to apply to all forms of relapse, and to the outcome of the disease, it would furnish justification from the standpoint of the individual for allowing all patients with early syphilis to go on to secondaries, build up their immunity reactions and thenceforth combine the immunity with the effects of treatment. This point is further discussed in connection with the effect at various stages of various systems of treatment. Rejection of such delay as a treatment policy must rest on the social consideration of the control of infectiousness in the large body of patients with early syphilis and on the fact that there is at least a slight advantage with reference to all other forms of relapse, in beginning treatment while the chancre is still seronegative. With reference to the seropositive chancre stage, the treatment outcomes, presently discussed, indicate that for the individual there may be a slight advantage in permitting him to go on to secondaries if continuous treatment is available.

When, however, the advantage of cutting off infectiousness in almost all patients with early syphilis as soon as they are seen is weighed against the costs, risks and some uncertainty attached to the immunizing process of developing secondaries in quarantine, there can be little doubt that immediate treatment of the early case, the earlier the better, is the socially wise policy, and one not productive of new and significantly increased dangers for the individual. But the physician must warn the seropositive primary patient that he must be doubly vigilant with regard to relapse, and, if anything, even more persistent in treatment than the patient who has developed secondaries. The treatment optimums on which this statement is based are presently discussed.

The Effect of the Amount of Treatment on Incidence of Relapse. In the new study (Table 2), it appears that there is a steady drop in the incidence of all forms of relapse with an increasing number of arsphenamin injections, except in the case of asymptomatic neurosyphilis and cardiovascular syphilis. Both these latter increased

in frequency (1.2% to 5.3% and 0.3% to 2.1%, respectively) as treatment increased. Whether or not this increase is to be entirely attributed to the presumption that more treatment will be given to patients showing signs of increased resistance or threatened complications or not—will be considered in connection with the 2-year results of treatment.

TABLE 2.—FREQUENCY OF RELAPSE IN PATIENTS TREATED AND OBSERVED IN THE EARLY STAGES OF SYPHILIS FOR ANY PERIOD OF TIME.

Type of relapse.	Amount of arsphenamin.					
	9 doses or less.	10 to 19 doses.	20 to 29 doses.	30 to 39 doses.	40 doses or over.	Total.
			Number.			
Early infectious:						
Mucocutaneous	314	66	27	3	1	411
Ocular	40	4	2	..	..	46
Central nervous system:						
Symptomatic	105	26	12	4	2	149
Asymptomatic	51	42	19	7	5	124
Benign, late	29	18	2	1	..	50
Cardiovascular	14	6	5	5	..	30
Visceral	2	..	..	..	..	2
Total cases relapsing	473	147	64	20	8	712*
Total cases	4094	1645	754	244	94	6831*
			Per cent.			
Early infectious:						
Mucocutaneous	7.7	4.0	3.6	1.2	1.1	6.0
Ocular	1.0	0.2	0.3	..	..	0.7
Central nervous system:						
Symptomatic	2.6	1.6	1.6	1.6	2.1	2.2
Asymptomatic	1.2	2.6	2.5	2.9	5.3	1.8
Benign, late	0.7	1.1	0.3	0.4	..	0.7
Cardiovascular	0.3	0.4	0.7	2.1	..	0.4
Visceral	0.05	..	..	..	..	0.02
Total cases relapsing	11.6	8.9	8.5	8.2	8.5	10.4
Total cases	100.0	100.0	100.0	100.0	100.0	100.0

* There were 24 cases having 2 relapses which fell in different treatment groups. The relapses were included in both places and, therefore, raised the totals in the total cases from 6807 to 6831 and 688 to 712.

Cases of Early Syphilis Under Treatment-Observation for 2 Years or More. *Results of Treatment-Observation.* "Satisfactory results" as here used includes all cases classified as "cured," with or without physical examination, probation, or reinfection, and those cases which had a "satisfactory result" although heavy metal therapy was continued long after this had been obtained. A "satisfactory

result" indicates a long series of negative blood serologic tests, in many cases a negative spinal fluid, no recent clinical or serologic signs of relapse or progression, and in most instances a negative physical examination.

In the series observed for 6 months or longer, 3244 cases, the "satisfactory results," using the criteria indicated above, reached 27.9%; in the 2-year or longer series, 1360 cases; this had increased to 52.7%. The increased proportion is probably due (1) to longer treatment in the better observed patients, or (2) to the fact that as time passes the tendency to relapse automatically declines and the disease is brought to a standstill. This proportion of arrest is compared in a subsequent paper with that to be expected of untreated cases as disclosed by Bruusgaard's study of Boeck's material.

Effect of Treatment Systems on the Proportion of Satisfactory Results. Let it be recalled that the proportions just given from Table 3 represent the aggregate of all methods of treatment: continuous, intermittent, irregular and intensive.* From Table 3 it now appears that, classified on the basis of the system of treatment employed and the stage of the disease in which treatment is begun, a consistent group of differences in results begins to appear. The 2-year satisfactory results in seropositive primary syphilis are consistently poorer than those obtained in seronegative primary syphilis regardless of system, and likewise poorer than in fully developed secondary syphilis *treated by a continuous system.* The results in secondary syphilis under intermittent, irregular and intensive treatment are, on the contrary, inferior even to those in seropositive primary syphilis. The lead of seronegative primary syphilis is, indeed, a notable one, and represents the best that modern methods have to offer—86.4% satisfactory results if treatment is continuously given to an infection identified by dark field before the blood test becomes positive. Once the blood test becomes positive, the proportion drops to 64.3%, even with continuous

* *Continuous treatment* is defined as uninterrupted treatment with an arsphenamin or a heavy metal, or both, whether administered in alternation or simultaneously, throughout treatment, including so-called "overlapping" treatment. The distinctive feature of this scheme is its *uninterrupted* character. In this group were included patients receiving prolonged treatment, even though its continuity was broken toward the last by a lapse.

Intermittent treatment is defined as treatment with an arsphenamin or heavy metal, or both, which is interrupted by short rest intervals throughout treatment, whether they are purposeful or not. The distinctive feature is the rest interval of 1 month or more duration.

Irregular treatment is defined as treatment with an arsphenamin or heavy metal, or both, which is absolutely irregular, no one of the systems heretofore described being consistently or even approximately followed.

Intensive treatment is defined as treatment with an arsphenamin or heavy metal, or both, which consists of short, intensive arsphenamin phases (3 to 4 injections in 3 to 8 days), alternating with a more or less prolonged heavy metal course of mercurial inunctions or intramuscular injections of mercury or bismuth (4 to 8 weeks or more) with purposeful rest intervals. (Ven. Dis. Inform., Washington, **13**, 209, 1932.)

treatment; but it rises again to only a little short of the seronegative group result, that is, to 81.5%, when the patient with secondaries is continuously treated.

TABLE 3.—CASES OF EARLY SYPHILIS TREATED OR OBSERVED FOR 2 YEARS OR MORE, SHOWING THE RESULT OF TREATMENT BY DIAGNOSIS ON ADMISSION AND THE SCHEME OF TREATMENT EMPLOYED.

Scheme of treatment.	Seronegative primary.		Seropositive primary.		Early secondaries.		Delayed secondaries.		Total.	
	Satisfactory results.*	All other outcomes.	Satisfactory results.*	All other outcomes.	Satisfactory results.*	All other outcomes.	Satisfactory results.*	All other outcomes.	Satisfactory results.*	All other outcomes.
					Number.					
Continuous	19	3	18	10	97	22	3	..	137	35
Intermittent	47	10	85	37	245	155	10	6	387	208
Irregular .	29	24	41	78	108	252	4	10	182	364
Intensive .	5	3	2	3	4	29	..	1	11	36
Total . .	100	40	146	128	454	458	17	17	717	643
					Per cent.					
Continuous	86.4	13.6	64.3	35.7	81.5	18.5	100.0	..	79.7	20.3
Intermittent	82.5	17.5	69.7	30.3	61.3	38.7	62.5	37.5	65.0	35.0
Irregular .	54.7	45.3	34.5	65.5	30.0	70.0	28.6	71.4	33.3	66.7
Intensive .	62.5	37.5	40.0	60.0	12.1	87.9	..	100.0	23.4	76.6
Total . .	71.4	28.6	53.3	46.7	49.8	50.2	50.0	50.0	52.7	47.3

* "Satisfactory results" includes all cases classified as cured, with or without a physical examination, probation or reinfection, and those cases which apparently had a satisfactory result although heavy metal treatment was continued long after one had been obtained (especially referable to Western Reserve cases).

It is unnecessary here to comment again on the further demonstration afforded by these figures, of the worth of continuous treatment and the progressively increasing ineffectiveness of the intensive and the irregular types of treatment. This has been supported by previous studies, and here merely receives confirmation. Without further discussion, then, a possible explanation for the differences in effect of treatment of all types in the seronegative and seropositive primary stages and of continuous treatment in the secondary stage may be sought.

First of all, it is apparent that treatment of any kind has an exceptional effect if applied in the seronegative primary stage. Seronegative primary syphilis in man must, indeed, be a rather easily responsive infection, relatively speaking, if totally irregular treatment can produce 54.7% satisfactory results. Bruusgaard finds the proportion of spontaneous cures to approximate 43%, so

that even irregular treatment increases the natural advantage of the bodily defense. The first element to be invoked, then, in a possible explanation of the observed variations in treatment effect at different stages, is that of intrenchment of the infection. The seronegative primary syphilis case responds readily to anything or almost nothing because the spirillicides and artificial stimulation of resistance by medication overwhelm the organism, still exposed and unadjusted to its new environment and unprotected from assault by fibroid tissue reaction. The seropositive primary case has lost this advantage of an exposed organism. It has not gained, in exchange, the advantage of its own constitutional reaction against the disease by the development of visible secondaries.

But if it is so much of an advantage theoretically to allow the patient to develop a constitutional and especially a cutaneous reaction to his infection, why is not this advantage manifest in the results of other forms of treatment than the continuous in the secondary stage? In explaining the discrepancy between continuous treatment results, on the one hand, and intermittent, irregular and intensive treatment, on the other, in secondary syphilis, the rest interval may again be invoked as the primary difference between the two groups, and the probable explanation of the greater effect of continuous treatment. This explanation would be satisfying on sight were it not for another observed discrepancy in Table 3. The effect of intermittent treatment in seropositive primary syphilis is slightly better than is that of continuous treatment. How can such an unexpected effect be explained?

It is conceivable that the biologic course of resistance development in syphilis will account for both phenomena. In seronegative primary syphilis the full effect of treatment is exerted upon the organism; the patient is cured by spirillicidal action, so to speak; during the early period of treatment, when in all probability the most significant blows are struck, his spontaneously developed resistance based on the presence of the organism plays little part. The proportion of satisfactory results, therefore, varies with the intensity and duration of application of the spirillicides; and since this is at its maximum with continuous treatment, and at its least with irregular treatment, the results vary accordingly. On the other hand, the patient once being in process of constitutional reaction to his infection, but short of its consummation, especially in the cutaneous phase, as he is in seropositive primary syphilis, every pause in treatment, every cessation of spirillicidal action permits, in theory, a revival of organisms and a new, if brief, stimulus to systemic reaction aginst the disease. Thus it may come about that intermittent treatment, with its pauses, permits the adding of some, even if small, increments of constitutional reaction and resistance to the effects of treatment. The ultimate outcome of spirillicide plus fractional resistance increments in rest

periods at this stage is a little better than if the patient had been obliged by a continuous system of treatment to fight his infection solely by spirillicidal means, introduced from without. Hence we witness, at a stage when bodily reaction, as indicated by serologic positiveness, has reached the point where it can add its effect to treatment, the curious paradox of an inferior method of treatment from the spirillicidal standpoint, producing superior ultimate results because its rest periods permit the addition to the patient's resources of some bodily resistance following revivals of the infection.

How shall such a group of considerations be applied to the equally curious situation of the patient with full cutaneous secondary reaction, who, if continuously treated, achieves a result almost equal to that obtainable in seronegative primary syphilis but falls to the lowest level of all in ultimate results if rest intervals are permitted at this stage, as in intermittent, intensive or irregular treatment? Here it may be presumed that the patient with secondaries has added the full force of his bodily reaction to the possibilities of whatever form of treatment he is given. Rest periods no longer mean for him increments of resistance, as they may in the seropositive primary patient who has not yet achieved his full cutaneous reaction. The effect of the method of treatment as such, therefore, again asserts itself, augmented by resistance factors but offset by tissue intrenchment of the organism in healing local tissue foci. Then, as in other aspects of early syphilis, including seronegative primary and the first 4 years of latency (Moore), continuous treatment asserts its primacy.

It is realized that an explanation involving so many incompletely explored areas as the concept of constitutional resistance to syphilis is not ready for standardized application in practice, particularly in the treatment of seropositive primary syphilis. Further observation and thought on the effect of a staggered or fractional resistance development as a substitute for postponement of treatment until secondaries appear is, however, justified as a possible future method of dealing with seropositive primary syphilis.

Conclusions. 1. The maximum frequency of relapse in early syphilis under observation and treatment 6 months or longer is 19.7% (mucocutaneous, 12.1%; asymptomatic neurosyphilis, 3.4%; symptomatic neurosyphilis, 4.1%; cardiovascular, 0.9%).

2. The incidence of mucocutaneous relapse is lowest in those patients who have had a full secondary reaction to the disease.

3. Patients who begin treatment in the seropositive primary stage have the highest incidence of mucocutaneous relapse.

4. Nonetheless, no advantage appears on other grounds in permitting a seropositive primary case to go on to secondaries.

5. The seropositive primary case must be treated with exceptional thoroughness.

6. Relapse decreases in frequency with an increasing number of

arsphenamin injections, except in the case of cardiovascular and asymptomatic neurosyphilis.

7. Satisfactory ("curative") treatment results are obtained in cases observed 2 years or longer (up to 20 years) in 52.7% of cases without respect to amounts and methods of treatment.

8. Treatment begun in seronegative primary syphilis (dark field diagnosis) by a "continuous" system yields 86.4% "satisfactory results."

9. The proportion of "satisfactory results" drops to 64.3% by the same method if the treatment is delayed until the serologic tests become positive.

10. If the patient has developed secondaries, the proportion of "satisfactory results" (2 years and after) again rises to 81.5% by a continuous system of treatment.

11. Other systems of treatment do not yield as satisfactory results. But in seronegative primary syphilis even irregular treatment yields 54.7% "satisfactory results."

12. The observed differences in treatment by various methods are discussed in terms of a theory of the function of resistance and the rest interval.

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WHAT TREATMENT IN EARLY SYPHILIS ACCOMPLISHES.

II. Optimum Treatment.

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In Paper I, case material of 1360 patients with early syphilis treated and observed for from 2 to 20 years was discussed from the standpoint of relapse and satisfactory or "curative" results. The difference in behavior of various phases of early syphilis and the results obtained by the scheme of treatment (continuous, *i. e.*, without rest intervals) producing the highest proportion of "cures" were discussed. The present paper takes up the definition of the amount of treatment required in various phases of early syphilis, the effect of arsphenamin dosage and of spinal fluid abnormality on

* Names with asterisk represent U. S. Public Health Service; names without asterisk represent the Coöperative Clinical Group.

outcome and the irreducible margin of failure with the methods of treatment employed in this series.

Optimum Amounts of Treatment. *Influence of the Number of Injections of Arsphenamin on Satisfactory Results.* It appears that the highest proportion (85%) of satisfactory results in seronegative primary syphilis is obtained in the group receiving 10 to 19 arsphenamin injections with accompanying heavy metal; in seropositive primary syphilis it requires 25 to 35 injections to produce the highest proportion of good results obtainable, namely, 65%. In early secondary syphilis, the highest proportion of good results is achieved by 20 to 29 injections (58%). In viewing the downward trend of good results as secondary syphilis develops it must be recalled that we are dealing in this table with all systems of treatment, and that intermittent and irregular schemes of treatment in secondary syphilis give the relatively poor showings which bring the proportion of good results down to 58%.

TABLE 4.—EARLY SYPHILIS TREATED OR OBSERVED FOR 2 OR MORE YEARS, SHOWING THE RESULT OF TREATMENT BY THE STAGE OF THE DISEASE AND THE AMOUNT OF ARSPHENAMIN ADMINISTERED.

Amount of arsphenamin.†	Seronegative primary.		Seropositive primary.		Early secondaries.		Delayed secondaries.		Total.	
	Satisfactory results.*	All other outcomes.	Satisfactory results.*	All other outcomes.	Satisfactory results.*	All other outcomes.	Satisfactory results.*	All other outcomes.	Satisfactory results.*	All other outcomes.
					Number.					
Little or no arsphenamin or heavy metal	..	1	3	6	1	3	..	..	4	10
9 doses or less	13	7	10	21	54	56	4	1	81	85
10 to 19	39	7	49	46	138	147	6	10	232	210
20 to 29	33	11	54	28	166	120	5	3	258	162
30 to 39	10	5	16	9	67	71	1	1	94	86
40 or over	5	9	12	18	23	54	1	1	41	82
Little or no arsphenamin and much heavy metal	..	..	2	..	5	7	..	1	7	8
Total	100	40	146	128	454	458	17	17	717	643
					Per Cent.					
Little or no arsphenamin or heavy metal	..	100.0	33.3	66.7	25.0	75.0	..	..	28.6	71.4
9 doses or less	65.0	35.0	32.3	67.7	49.1	50.9	80.0	20.0	48.8	51.2
10 to 19	84.8	15.2	51.6	48.4	48.4	51.6	37.5	62.5	52.5	47.5
20 to 29	75.0	25.0	65.9	34.1	58.0	42.0	62.5	37.5	61.4	38.6
30 to 39	66.7	33.3	64.0	36.0	48.6	51.4	50.0	50.0	52.2	47.8
40 or over	35.7	64.3	40.0	60.0	29.9	70.1	50.0	50.0	33.3	66.7
Little or no arsphenamin and much heavy metal	..	..	100.0	..	41.7	58.3	..	100.0	46.7	53.3
Total	71.4	28.6	53.3	46.7	49.8	50.2	50.0	50.0	52.7	47.3

* "Satisfactory results" includes all cases classified as cured, with or without a physical examination, probation or reinfection, and those cases which apparently had a satisfactory result although heavy metal treatment was continued long after one had been obtained (especially referable to Western Reserve cases).

† Number of injections of arsphenamin used as the measure of treatment, practically all cases were treated with accompanying heavy metal.

Table 4 presents a series of very interesting aggregates. Relating the number of arsphenamin injections to the stage of the disease at which treatment was begun, the point observed in previous studies, it again appears that the higher number of injections apparently leads to a smaller proportion of satisfactory results than some of the smaller amounts of treatment. Table 5, subsequently discussed, goes far to show that the reason patients receiving the larger number of injections get less satisfactory results is because their infections have in their course shown evidence of unusual resistance, and they have accordingly been given more treatment in the effort to overcome the resistance.

It is apparent again that the seropositive primary stage is the more resistant and requires a larger amount of treatment for the achievement of the best possible results than does seronegative primary syphilis. A greater tendency to relapse or to show various other signs of resistance demands of the patient greater persistence in treatment and a larger total amount of treatment, although with this increased treatment better results are obtained than with similar amounts after syphilis has reached the secondary stage.

That the numbers of injections, regardless of system, given as optimums in the previous paragraph, are not to be regarded as inflexible or universally applicable routine, appears from the analysis of Table 5. From this table it may be seen that even inadequately treated syphilis (less than 20 injections of arsphenamin with heavy metal) yields its proportion of satisfactory results (66%) in patients who were treated for 2 years and never subsequently, yet never received in all more than 20 doses of arsphenamin. The adequately treated patients (more than 20 injections of arsphenamin with heavy metal in the same period) gained only 11% by the adequacy of their treatment. The sharp drawing of the line between adequacy and inadequacy at 20 arsphenamin injections, of course, increases the good results under "inadequate treatment," for Table 4 shows that at least the seronegative primary cases attain their highest proportion of good results from 10 to 19 injections.

As soon as our material is divided into two groups, one in which treatment was suspended at the end of 2 years, and the other in which treatment was continued after 2 years, the analysis of the clinical behavior of each group indicates that those treated for the longer time *did* show clinical and serologic evidence of greater resistance. Even in the adequately treated cases treated after the second year it appears that serologic relapse occurs in 12.6% as against 6% in those whose treatment was not carried beyond the second year. Irreversible Wassermann reactions were present in those treated beyond the second year in 7%, while in those not treated beyond the second year they were present in only 1.7%. The same proportion holds true for neurorelapse and resistant asymptomatic neurosyphilis. It is presumed that patients were

continued on treatment beyond the second year because they showed clinical or serologic signs of resistant infections. The only method of examining the validity of this presumption, possible in this study, which would tend to show that the excessive treatment had a share in producing the resistance of the infection and the lower proportion of good results with the higher number of arsphenamin injections, would be by way of an analysis of the effect of arsphena-

TABLE 5.—FINAL RESULTS OBTAINED IN EARLY SYPHILIS WITH A COMPARISON OF THOSE ADEQUATELY AND INADEQUATELY TREATED DURING THE FIRST 2 YEARS OF THE INFECTION.

Final results of treatment.	Treatment given during the first 2 years of infection.							
	Adequate.*				Inadequate.*			
	No subsequent treatment.		Subsequent treatment.		No subsequent treatment.		Subsequent treatment.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cen.
Grand total, all outcomes	232	100.0	301	100.0	198	100.0	629	100.0
Satisfactory outcome	179	77.2	148	49.2	131	66.2	259	41.2
All other outcomes	53	22.8	153	50.8	67	33.8	370	58.8
Improving when last seen	25	10.8	73	24.3	22	11.1	152	24.2
Relapse: Serologic	14	6.0	38	12.6	20	10.1	86	13.7
Clinical	5	2.2	9	3.0	7	3.5	31	4.9
Irreversible blood	4	1.7	21	7.0	16	8.1	94	14.9
Neurosyphilis	4	1.7	22	7.3	8	4.0	41	6.5
Spinal fluid fast	1	0.4	9	3.0	1	0.5	10	1.6
Dead	5	2.2	3	1.0	4	2.0	5	0.8

* Adequate treatment consists of 20 or more doses of an arsphenamin with accompanying heavy metal; inadequate treatment less than this amount.

TABLE 6.—EFFECTIVENESS OF SIZE OF DOSE OF OLD ARSPHENAMIN IN PATIENTS FOLLOWED FOR 2 YEARS OR MORE, WHO RECEIVED 20 OR MORE DOSES OF ARSPHENAMIN WITH PROPORTIONATE AMOUNT OF HEAVY METAL.

Scheme of treatment.	Total cases.		Satisfactory outcome.		Improved.		Unsatisfactory outcome.		Relapse or resistant serum.		Clinical relapse.		Neurosyphilis, CSF fast.		Dead.	
							Size of dose.*									
	Small.	Large.	Small.	Large.	Small.	Large.	Small.	Large.	Small.	Large.	Small.	Large.	Small.	Large.	Small.	Large.
	Number.															
Continuous	66	25	55	24	1	..	6	..	5	..	4	..	..	..	4	1
Intermittent	157	95	94	55	38	23	24	16	19	11	4	3	13	3	1	1
Irregular	109	73	42	16	31	27	34	30	24	25	5	4	17	7	2	
Total	332	193	191	95	70	50	64	46	48	36	13	7	30	10	7	2
	Per cent.															
Continuous	100	100	83.3	96.0	1.5	..	9.1	..	7.6	..	6.1	..	..	..	6.1	4.0
Intermittent	100	100	59.9	57.9	24.2	24.2	15.3	16.8	12.1	11.6	2.5	3.2	8.3	3.2	0.6	1.1
Irregular	100	100	38.5	21.9	28.4	37.0	31.2	41.1	22.0	34.2	4.6	5.5	15.6	9.6	1.8	
Total	100	100	57.5	49.2	21.1	25.9	19.3	23.8	14.5	18.7	3.9	3.6	9.0	5.2	2.1	1.0

* Size of dose: Males: small, 0.2 to 0.45; large, 0.45 or over. Females: small, 0.2 to 0.3; large, 0.3 or over.

min dosage on outcome. If it can be shown that a higher proportion of good results attends the use of the lower doses of arsphenamin as against the higher, a counterpresumption may be established that at least a part of the less favorable results in the higher-number series is attributable to overuse of the drugs rather than merely to virulence of the disease. This question is examined in Table 6.

In examining the effect of arsphenamin dosage (restricted to "606") on the relatively less favorable outcomes of patients who received the longer series of injections (over 20) the scale of dosage rated as "small" (Table 6) is from 0.2 to less than 0.45 gm. for males and 0.2 to less than 0.3 gm. for females. "Large dosage" is 0.45 gm. or over for men and 0.3 gm. or over for women. On the basis of such a partition, not wholly satisfactory, to be sure, with so small a sample, and the disregard of body weight, on which there were only limited data in this series of cases, it appears that *there is nothing to indicate that large dosage causes any type of unfavorable outcome* when either continuous or intermittent treatment is used. On the other hand, *there is distinct evidence that small dosage has definite shortcomings.* With continuous treatment there is not a single unsatisfactory outcome (deaths not due to syphilis or treatment) on the higher dosage scale. But on the lower dosage scale, 7.6% relapsed or were resistant serologically; 6% had clinical relapses; none had neurosyphilis on either scale. Intermittent treatment shows practically no difference between the dosage scales, except in the matter of neurosyphilis in which the lower dosage scale showed 8.3% as against 3.2% for the higher dosage scale. *These findings not only point out the need for the higher dosage scale, but explicitly negate the idea that arsphenamin as such predisposes to neurosyphilis.* It will be noted that the apparent advantage of the smaller dosage when treatment is irregularly given is confined to a lower per cent of relapse or resistant serologic findings. Even with the irregular treatment scheme the more significant type of unsatisfactory outcome, that of neurosyphilitic involvement, is higher with the small than with the large dosage scale.

We may say, then, that the apparent reduction in good results with prolongation of treatment is not due to the unfavorable effect of a prolonged use of arsenicals. In fact, the evidence points to the desirability of a higher scale of dosage of these drugs than some employed at the present day, at least within the field of the treatment techniques used in early syphilis by the coöperating clinics, in which courses of heavy metal alternate with the arsenical.

Effect of Spinal Fluid Abnormality on Treatment Outcome. Many groups of reported results of treatment for syphilis are notably deficient in that there was no satisfactory control of the spinal fluid. In this series, spinal fluid control was exercised in 1090 patients, or 80%, of the 1360 patients under observation or treatment for 2 years or more. Of the 1090 patients, 33% (365) showed some degree of spinal fluid abnormality. The base line was 65% of

satisfactory results when the spinal fluid was negative. When the cell count was 6 or over, and all other findings negative, the satisfactory results in this group dropped to 62%. When the cell count was 5 or over and protein was increased but the Wassermann and colloidal tests were negative, the satisfactory results dropped to 35%. When the cell counts and Wassermann test were positive and the protein and colloidal tests positive or negative, the proportion of satisfactory results under all varieties of treatment aggregates only 28%; and in cases with a definitely abnormal spinal fluid classified as Group III (paretic formula) only 9% of such patients obtained a satisfactory result. Analyzed with respect to the influence of treatment method on result in these cases, it was found that irregular treatment was the principal factor in causing an abnormal spinal fluid.

Regardless of the perplexities introduced into the question of optimums in Table 4, it is impossible to escape the clearness of the demonstration which it affords; that *adequate treatment for early syphilis within the first 2 years, in each and every category of course and outcome, yields substantially better results than does inadequate treatment, by whatever method. More than 20 arsphenamin injections is better than less than 20 arsphenamin injections, each with the accompanying heavy metal.*

Moreover, it further deserves emphasis, that there is no deadline drawn at 2 years for the patient who has received inadequate treatment within that period. Even granted that he does not achieve a satisfactory result within this ideal period, it is worthwhile to go on. Table 7 expressly examines this question, with the following results. Of those patients who had had inadequate treatment within the first 2 years of their infection (less than 20 arsphenamin injections with the accompanying heavy metal), 33% will ultimately become symptom-free and serologically negative with further treatment. What form shall this further treatment take? It is notable that it should not be merely a continuation of heavy metal therapy, *but a further administration of the arsphenamin.* If heavy metal alone was given, only 18% of the patients so treated were reclaimed. If 10 or less injections of an arsphenamin were also given, 24% were reclaimed. If *more* than 10 injections of an arsphenamin were given in conjunction with the continued heavy metal, 50% of the unsatisfactory results were brought to a serologic and clinical negativity. In the categories of serologic and neurorelapse following inadequate treatment, this statement was borne out. The group of patients adequately treated during the first 2 years tends to bear out the same contention, though in much less striking fashion. Representing possibly an even higher degree of resistance which probably led to their better adherence to treatment schedule, they became symptom-free after the first 2 years by the continued use of heavy metal in 30% of cases. If more than 10 injections of an arsphenamin were added,

the proportion was raised to 58%. *The resistant patient with early syphilis should, then, be treated not with heavy metal alone, but with heavy metal plus 10 or more injections of an arsphenamin in addition to those which he received in the 2-year period.*

TABLE 7.—TYPE OF UNSATISFACTORY OUTCOME AT THE END OF THE FIRST 2 YEARS OF TREATMENT OF EARLY SYPHILIS WITH THE PATIENT'S RESPONSE TO FURTHER TREATMENT.

Cases having an unsatisfactory result at end of first 2 years, showing amount of subsequent treatment.	Adequate treatment during first 2 years.					Inadequate treatment during first 2 years.				
	Final outcome.									
	Total.	Serologically and clinically negative.		Unsatisfactory.		Total.	Serologically and clinically negative.		Unsatisfactory.	
		No.	Per cent.	No.	Per cent.		No.	Per cent.	No.	Per cent.
Unsatisfactory, receiving:										
Heavy metal only	10	3	30.0	7	70.0	28	5	17.9	23	82.1
10 arsenicals or less	42	5	11.9	37	88.1	143	34	23.8	109	76.2
Over 10 arsenicals	33	19	57.6	14	42.4	102	51	50.0	51	50.0
Total	85	27	31.8	58	68.2	273	90	33.0	183	67.0
Serologic relapse or resistant serum, receiving:										
Heavy metal only	9	2	22.2	7	77.8	22	4	18.2	18	81.8
10 arsenicals or less	36	5	13.9	31	86.1	137	33	24.1	104	75.9
Over 10 arsenicals	25	16	64.0	9	36.0	82	40	48.8	42	51.2
Total	70	23	32.9	47	67.1	241	77	32.0	164	68.0
Clinical relapse, receiving:										
Heavy metal only	2	..	...	2	100.0					
10 arsenicals or less	8	2	25.0	6	75.0	29	9	31.0	20	69.0
Over 10 arsenicals	9	8	88.9	1	11.1	37	21	56.8	16	43.2
Total	19	10	52.6	9	47.4	66	30	45.5	36	54.5
Neurosyphilis and spinal fluid fast, receiving:										
Heavy metal only	2	1	50.0	1	50.0	7	1*	14.3	6	85.7
10 arsenicals or less	10	..	...	10	100.0	20	6	30.0	14	70.0
Over 10 arsenicals	16	8	50.0	8	50.0	25	10	40.0	15	60.0
Total	28	9	32.1	19	67.9	52	17	32.7	35	67.3

* This case also had intraspinal treatment.

Granted this point in the management of the resistant early case, is there any justification for the arbitrary continuation of treatment beyond the 2-year period on a species of "general principles," in the patient who has achieved a satisfactory result within the 2-year period? To this, Table 8 contributes some significant information. It appears that in patients clinically and serologically negative at the end of the first 2 years, whether their previous treatment has been adequate (more than 20 arsphenamin injections with the accompanying heavy metal) or inadequate, the proportion

who ultimately relapse or progress into some form of unsatisfactory outcome, regardless of further treatment or not, is only 4.1% for the adequately treated, and 3.7% for the inadequately (533 and 827 cases, respectively). This is tantamount to saying that an uneventful course toward serologic and clinical negativity within 2 years is a species of promise for the future, and has a margin of error, so to speak, of only 4%. Within this margin of error, the highly practical desideratum of a point at which to stop and to substitute observation for further treatment may be defined. *An uneventful course toward recovery justifies the parole of the patient to observation after 2 years of adequate treatment.* To add further stress to the emphasis which adequate as contrasted with inadequate treatment deserves, it may be pointed out that (Table 8) 76% were in the satisfactory classification at the termination of all treatment if they had been adequately treated, while only 57% were in that classification if their first 2 years of treatment had been inadequate.

TABLE 8.—FINAL OUTCOME IN RESISTANT CASES OF EARLY SYPHILIS, SHOWING THE EFFECTIVENESS OF SUBSEQUENT TREATMENT AFTER THE FIRST 2 YEARS OF TREATMENT.

Result at end of first 2 years.	Adequate treatment during first 2 years.				Inadequate treatment during first 2 years.			
	Final Outcome							
	Serologically and clinically negative.		Unsatisfactory.		Serologically and clinically negative.		Unsatisfactory.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Serologically and clinically negative:								
No further treatment	206	38.6	4	0.8	153	18.5	2	0.2
Heavy metal only	105	19.7	4	0.8	146	17.7	7	0.8
1 to 10 arsenicals	72	13.5	5	0.9	137	16.6	15	1.8
More than 10 arsenicals	20	3.8	9	1.7	35	4.2	7	0.8
Total	403	75.6	22	4.1	471	57.0	31	3.7
Unsatisfactory:								
No further treatment	..	..	22	4.1	..	..	43	5.2
Heavy metal only	3	0.6	7	1.3	5	0.6	23	2.8
1 to 10 arsenicals	5	0.9	37	6.9	34	4.1	109	13.2
More than 10 arsenicals	19	3.6	14	2.6	51	6.2	51	6.2
Total	27	5.1	80	15.0	90	10.9	226	27.3
Total cases*	533				827			

* There were 10 cases where the result of treatment at the end of 2 years was unknown.

The irreducible residue of failure from apparently satisfactory results in the earlier observation periods is 3.7% to 4.1%. From the earlier unsatisfactory result groups the irreducible minimum of

ultimate poor results is 15% with early adequate treatment and 27% with inadequate treatment during the first 2 years. From this statement the fact stands out clearly that syphilis partitions its victims from the outset into "sheep" and "goats," and that taking good treatment and bad, in the aggregate the "goats" will range from 4% to 27%. These percentages may then be thought of as representing the morbidity of syphilis under present-day treatment conditions.

Conclusions. 1. Disregarding treatment systems, the highest proportion of "satisfactory results" in seronegative primary syphilis was obtained with 10 to 19 (preferably the higher number) injections of arsphenamin (with accompanying heavy metal); in seropositive primary syphilis, 25 to 35 injections; in early secondary syphilis (first year), 20 to 29 injections. The good result obtainable with the prolongation of treatment in seropositive primary syphilis is apparent.

2. The proportion of satisfactory results thus obtained for the respective phases is 85%, 65% and 58%, respectively, regardless of system.

3. Poorer results in prolonged treatment are due to the intrinsic resistance of the case, not to the prolongation of treatment.

4. The use of a higher arsphenamin ("606") dosage scale exerts no unfavorable effect on outcome. In fact, there is evidence that a low-dosage scale has definite shortcomings.

5. Neurosyphilitic relapse is higher on a low-dosage than a high-dosage scale when intermittent (rest interval) treatment is used.

6. Arsphenamin adequately used does not predispose to neurosyphilis.

7. Satisfactory treatment results decline from 62% to 9% with progressively increasing grades of neurosyphilitic involvement as indicated by the spinal fluid findings (1090 cases).

8. More than 20 arsphenamin injections with accompanying heavy metal in the first 2 years of syphilis is better than less than 20 injections with heavy metal regardless of system.

9. Failure to get a satisfactory result by 20 injections or less calls for further administration of the arsphenamin. The giving of more than 10 additional injections plus heavy metal may double the proportion of unsatisfactory outcomes reclaimed.

10. In the decision as to when to stop treatment in the ordinary case, an uneventful clinical and serologic course toward recovery is paramount. In such an uneventful course, the parole of the patient to observation after 2 years of adequate treatment is justified.

11. The irreducible margin of failure in the treatment of early syphilis—the proportion of patients not likely to achieve or maintain a satisfactory result by any treatment—ranges from 4% to 27%, depending on method, stage at which treatment begins, adequacy of treatment during the first 2 years of the infection and other considerations discussed in previous papers.

WHAT TREATMENT IN EARLY SYPHILIS ACCOMPLISHES.†

III. COMPARISON OF BRUUSGAARD'S WORK AND THE 3- TO 20-YEAR RESULTS OF THE COÖPERATIVE CLINICAL GROUP.

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THE material in early syphilis, treated and observed for 3 or more years by the American Coöperative Clinical Group provides an exceptional background against which to project the outcome of untreated early syphilis as presented in Bruusgaard's remarkable evaluation of Cesare Boeck's series of patients untreated by specific methods between the years 1891 and 1910. The syphilis clinic at the Oslo Hospital with which Bruusgaard is connected serves a stable, well-educated population; it has for years been staffed by competent physicians, and between the years 1891–1916 its chief, Dr. Boeck, believed that patients with early syphilis did about as well without any treatment as with the mercurial therapy then in vogue. In these years, 2181 patients diagnosed as primary or secondary syphilis were admitted to the Oslo Clinic. Most of them received no treatment. Some received a little mercury by mouth or potassium iodid or both, but for all practical purposes it can be said that these patients were untreated, or practically so. In the years 1925–1927, Bruusgaard was successful in following 473 of the original 2181 patients; 309 were living and each of these was completely reëxamined physically with special emphasis on the cardiovascular and nervous systems, though routine examination of the cerebrospinal fluid was not carried out. Most of the 164 dead had died in the Oslo Hospital, the cause of death being known; in 40, necropsies had been obtained. The majority of the patients were reëxamined or had died more than 20 years after infection. Only 37% of the total number had developed any active lesion of late syphilis; 22% had died of some unrelated cause, and nearly half of this group had lived for 20 or more years after infection without developing any lesion. In 14% the only evidence of infection was a persistently positive blood Wassermann; in 27 per cent, clinical "arrest" or "cure" seemed to have occurred in spite of the absence of treatment.

With a view to making the appropriate comparisons, the material of the American study was recast into the categories employed

* Names with asterisk represent the U. S. Public Health Service; names without asterisk represent the Coöperative Clinical Group.

† Reference to previous publications by this group is given in a footnote to Part I.

by Bruusgaard. Barring any items of statistical disparity in that our group of 3- to 10-year cases is 821 in number in contrast with Bruusgaard's 79, and that we are unable to make precise comparisons of cardiovascular examination technique in the two groups, the two series of living patients stand parallel analysis very well. The notable thoroughness and extended range of Bruusgaard's physical examinations compensate to some degree for the comparative lack of spinal fluid studies, and his radiography of the heart and great vessels makes conclusions in the cardiovascular field fairly safe. Our 10-to 12-year group numbers 86, as compared with his 66 patients; our total number of cases considered, 907 (13.3% of our 6807 early syphilis patients) as compared with his 145 patients living at the time of the examination (6.6% of his total of 2181 patients with early syphilis).

It should be explained that Bruusgaard's inclusion of tabetic and paretic residua as syphilis was reduplicated in our own series, but that, as with Bruusgaard, all other scars or residua of the disease were excluded from the category of active syphilis. In the category of cardiovascular syphilis it is possible that the lack of definition of signs and symptoms accepted as evidence of involvement modifies the results in the living patients, for Bruusgaard's series includes a number of patients who had long shown signs of this type of involvement, while the shift in our clinical material has tended in the later years toward earlier recognition of symptoms and signs on the basis of routine periodic clinical examination.

The comparison of deaths has been excluded from the study because the procedure for the collection of the data on deaths varied in the two series. Bruusgaard followed his patients through the vital statistics office of Denmark, securing the cause of death in every possible case. The Coöperative Clinical Group did not make a similar effort through the vital statistics office of each of the states of the United States. The only cases of death which are recorded in the Coöperative Clinical material are those found through the social service follow-up of patients who lapsed from treatment before the maximum benefit had been received, or those who died within the institution of which the clinic treating the patient in the early stage of syphilis was an integral part. Deaths among those patients who had received an adequate amount of antisyphilitic treatment and been serologically and clinically negative for one year or more are unknown, unless before death it had happened that the patient had returned to the clinic treating his early syphilis with some late manifestation of the disease. That Bruusgaard's efforts were more effective in collecting data on deaths than those of the Coöperative Clinical Group is apparent from the proportion of deaths from all causes among his cases. In the 3- to 10-year material, Bruusgaard found 14 deaths per 100 cases as against 1 among the early cases treated by the Coöperative Clinical Group. In the

10- to 20-year material there were only 2 deaths from any cause recorded in the Coöperative Clinical material of 88 cases of syphilis as compared with 58 in 124 cases in the Bruusgaard material. However, since 14 of the 58 deaths in 124 patients in Bruusgaard's 10- to 20-year material had a cardiovascular or central nervous system involvement, whereas there was only 1 death from cardiovascular syphilis and none from central nervous system syphilis in the 88 cases of syphilis followed by the Coöperative Clinics for a similar period of time, one might safely assume that early and adequate treatment certainly has had at least a tendency to prolong life and to some extent control the late manifestations of syphilis. On the other hand, the good results obtained among the living patients in our series are at a minimum. The living patients in the Coöperative Clinical Group material, who remained under treatment or observation for 3 to 10 or 10 to 20 years, consist largely of those whose syphilis was of a relapsing or resistant type or those who had received inadequate and irregular treatment during the early stage of syphilis. Those patients who had responded well to treatment had to a large extent disappeared. For example, a third of the patients who had been under observation or treatment for 2 years were lost sight of by the beginning of the third year. Bruusgaard's follow-up and reëxamination of every available patient gives the end results of untreated syphilis the benefit of all readily responsive infections. Therefore, any evidence of good results in the Coöperative Clinic cases represents the very minimum of the effectiveness of treatment in controlling syphilis. With these considerations in mind we take up Table 9.

TABLE 9.—THE OUTCOME IN TREATED AND UNTREATED EARLY SYPHILIS (BASED ON LIVING PATIENTS ONLY).

Status of patient at time of final examination.	Treated cases in 5 cooperating clinics in the U. S.				Bruusgaard's analysis of Boeck's untreated cases.			
	Interval between infection and final examination.				Interval between infection and final examination.			
	3 to 10 years.		10 to 20 years.		3 to 10 years.		10 to 20 years.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Neurosyphilis	11	1.4	8	9.3	4	5.1	11	16.7
Cardiovascular:								
Definite	6	0.7	5	5.8	..	..	1	1.5
Suspicious	10	1.3	4	4.6				
Skin, mucosal or bone syphilis	16	2.0	1	1.2	27	34.2	21	31.8
Symptom-free with:								
Positive Wassermann	144	17.6	14	16.3	29	36.7	9	13.6
Negative Wassermann	634	77.0	54	62.8	19	24.0	24	36.4
Total	821	100.0	86	100.0	79	100.0	66	100.0

In Table 9, Bruusgaard's 3- to 10- and 10- to 20-year observation groups of living patients are paralleled with ours. Clinical neuro-

syphilis appears in 1.4% of our 3- to 10-year group; in his untreated cases in 5.1% within the same period. In our 10- to 20-year group it appears in 9.3% as compared with 16.7% of his untreated cases. There can be no question in this field of the worth of treatment.

Late skin, mucosal and bone syphilis appears in our treated 3- to 10-year group in 2% of cases; in Bruusgaard's in 34.2%. In the 10- to 20-year group our material shows 1.2%; Bruusgaard's 31.7%. This is an interesting commentary on the way in which modern treatment has done away with benign symptomatic syphilis. It is also discussable in the light of Brown and Pearce's theory of the rôle of reaction in bone and skin as a form of systemic defense in syphilis.

In the symptom-free but Wassermann-positive category our series includes 17.6% after 3 to 10 years; Bruusgaard's series 36.7%. In the 10- to 20-year group, we have 16.3%; he has 13.6%. Our figures suggest that we are dealing in the 10th to the 20th year with our irreducible minimum of fixed positive asymptomatic cases, which is almost identical with his group without treatment.

In the symptom-free Wassermann-negative group we have 77%, while Bruusgaard has only 24% in the 3- to 10-year period, and 62.8% as compared with 36.4% in the 10- to 20-year period. Inasmuch as these constitute, so far as present-day criteria go, the "cured" patients, the vindication of modern treatment methods within the limitations of this investigation is complete.

TABLE 10.—SPINAL FLUID EXAMINATIONS ON PATIENTS WITH EARLY SYPHILIS CLASSIFIED AS SYMPTOM-FREE, BLOOD WASSERMANN POSITIVE OR NEGATIVE AT TERMINATION OF TREATMENT (BASED ON LIVING PATIENTS ONLY).

Spinal fluid examination on termination of treatment.	Interval between infection and final examination.			
	3 to 10 years.		10 to 20 years.	
	No.	Per cent.	No.	Per cent.
Symptom-free, positive Wassermann.				
Spinal fluid:				
Not made	39	4.8	2	2.3
Negative	68	8.3	9	10.5
Positive during treatment, negative at end	8	1.0		
Positive at end of treatment	19	2.3	2	2.3
Positive during treatment, unknown at end	10	1.2	1	1.2
Total cases symptom-free, positive Wassermann:				
Coöperating Clinics	144	17.6	14	16.3
Boeck's cases	29	36.7	9	13.6
Symptom-free, negative Wassermann.				
Spinal fluid:				
Not made	97	11.8	9	10.5
Negative	454	55.3	41	47.8
Positive during treatment, negative at end	48	5.8	2	2.3
Positive at end of treatment	12	1.5	1	1.2
Positive during treatment, unknown at end	23	2.8	1	1.2
Total cases symptom-free, negative Wassermann:				
Coöperating Clinics	634	77.2	54	62.8
Boeck's cases	19	24.0	24	36.4

It is now essential to point out, though another tabular study is necessary to do so (Table 10), that had spinal fluid examinations been performed in an equally large proportion of Bruusgaard's patients as compared with our own, the blood serologic groups just discussed would have sustained a slightly different interpretation. Of the seropositive patients in our series, 2.3% have been aligned with the neurosyphilitic group in both the 3- to 10- and 10- to 20-year periods by examination of the spinal fluid. It is impossible to guess how many of Bruusgaard's untreated patients would have fallen in the same category (asymptomatic neurosyphilis). Among the seronegative patients in our series, even 1.5% and 1.2% of abnormal spinal fluids appeared at final examination after 3 to 10 and 10 to 20 years, respectively.

Bruusgaard found no cardiovascular syphilis in untreated patients (living) in the 3- to 10-year group, and only 1.5% in the 10- to 20-year period. In the 20- to 30-year Bruusgaard group, 10% appears, and in the 30- to 40-year group, 12.5%. We have, of course, no comparable groupings for the later years, but for the 3- to 10-year period 0.7% of cardiovascular syphilis is definitely recognized, and 1.3% of suspicious cases (dilated aorta by Roentgen ray). In the 10- to 20-year period we recognize 5.8% definitely and 4.6% as open to suspicion, where Bruusgaard finds only 1.5%.

Whether these rather marked differences are entirely ascribable to differences in examination technique, or whether we are witnessing here a genuinely predisposing or at least hastening effect of treatment, it is impossible from this material to say. As has been previously suggested, there is reason to think from Bruusgaard's description of his material that his cardiovascular cases were usually recognized at a later stage than ours.

With the reservations already set forth with regard to deaths in mind, as well as the fact that we have too small a statistical sample in either material from which to draw any definite conclusions, it is still worth while to observe that in the 3- to 10-year period Bruusgaard averages 1 death, with a definite cardiovascular involvement per 100 cases of syphilis, as compared with our 1 death, with a cardiovascular involvement in 500 cases of syphilis. In the 10- to 20-year period there were no deaths with a cardiovascular involvement in the 88 cases of syphilis treated and observed in our clinics, as compared with 10 deaths per 100 cases in Bruusgaard's series.

We have undertaken to examine Bruusgaard's classifications of his cases as applied to our own material, in terms of the various types of treatment which our patients received, in order to see whether principles such as we have recognized in previous studies apply with equal force to his typing of material in long periods of observation (over 3 years).

It appears that under "inadequate treatment" (less than 20 injections of arsphenamin and the accompanying heavy metal),

93% of our patients in the 3- to 10-year group achieved freedom from symptoms with a positive or negative Wassermann, while 60.7% of Bruusgaard's patients, untreated, achieved the same status. In the 10- to 20-year period, 85% of our patients achieved this same status, as against 50% of Bruusgaard's. Thus, even inadequate treatment holds a substantial lead over no treatment in the comparisons of these two series.

Adequate treatment in the 3- to 10-year period gave 96% symptom-free with Wassermann positive or negative for our series, while Bruusgaard's series shows 60.7%. In the 10- to 20-year period, treated cases stand at 74%, untreated at 50%. In Table 11 is given the classification on the basis of adequate and inadequate treatment by the continuous, intermittent and irregular schemes.

TABLE 11.—THE OUTCOME OF ADEQUATELY AND INADEQUATELY TREATED EARLY SYPHILIS BY THE CONTINUOUS, INTERMITTENT AND IRREGULAR SCHEMES OF TREATMENT FOR PATIENTS UNDER TREATMENT OR OBSERVATION FROM 3 TO 20 YEARS IN THE 5 COÖPERATING CLINICS IN THE UNITED STATES (BASED ON LIVING PATIENTS ONLY).

Status of patient at time of final examination.	1 to 19 doses of arsphenamin with heavy metal.						20 or more doses of arsphenamin with heavy metal.					
	Continuous.		Intermittent.		Irregular.		Continuous.		Intermittent.		Irregular.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
3 to 10 years.												
Neurosyphilis	1	2.4	1	0.7	6	2.9	..	..	1	0.5	2	1.2
Cardiovascular:												
Definite	..	..	..	..	3	1.4	..	..	..	..	3	1.8
Suspicious	1	2.4	1	0.7	2	1.0	2	3.2	4	2.0		
Skin, mucosal or bone syphilis	..	..	1	0.7	11	5.3	1	1.6	1	0.5	2	1.2
Symptom-free:												
Positive Wassermann	8	19.0	13	9.3	64	30.8	3	4.7	23	11.2	33	20.3
Negative Wassermann	32	76.2	124	88.6	122	58.6	57	90.5	176	85.8	123	75.5
Total	42	100.0	140	100.0	208	100.0	63	100.0	205	100.0	163	100.0
10 to 20 years.												
Neurosyphilis	..	..	..	..	2	7.4	..	..	..	..	6	14.3
Cardiovascular:												
Definite	..	..	..	..	2	7.4	..	..	..	..	3	7.1
Suspicious	..	..	..	..	1	3.7	..	..	..	..	3	7.1
Skin, mucosal or bone syphilis	..	..	..	..	1	3.7						
Symptom-free:												
Positive Wassermann	1	33.3	..	..	6	22.2	..	..	1	20.0	6	14.3
Negative Wassermann	2	66.7	9	100.0	15	55.6	..	..	4	80.0	24	57.2
Total	3	100.0	9	100.0	27	100.0	..	..	5	100.0	42	100.0

The analysis of this material (Table 11) on the basis of system of treatment, in both the inadequate and adequate groups, shows very clearly that it is irregular treatment which is largely responsible for the unsatisfactory outcomes. For example, in the 3- to 10-year period among inadequately treated patients, neurosyphilis, cardiovascular syphilis, and especially late skin, mucosal and bone

syphilis, occur mainly in the group of irregularly treated patients. In the 10- to 20-year period, they occur exclusively in patients whose treatment has been irregular.

The significance of the symptom-free Wassermann-positive group of patients, which one would ordinarily hesitate to admit to the category of benign or innocent syphilis, could not be discussed from Bruusgaard's cases owing to the lack of spinal fluid examinations in his series. It interested us, however, to see how relatively small a proportion of such cases after 3 to 20 years had abnormal fluids under either inadequate or adequate treatment. In the former case only 1.5% had abnormal fluids, while after adequate treatment 3% were abnormal. The presumption that the adequately treated cases were on the whole the more resistant applies here. It is, however, borne out here, as in the previous discussion, that by far the largest part of the spinal fluid abnormalities fall in the group of irregularly treated cases.

The examination of the symptom-free seronegative group which passes usually as clinical and serologic cure in most reports, shows that even freedom from symptoms and a negative blood do not invariably mean a normal spinal fluid. In the 3- to 10-year group, adequately but irregularly treated, there will be as high as 4.5% of patients who have abnormal spinal fluids in spite of their negative bloods and freedom from symptoms.

Summary. 1. A comparison is made of 907 cases of treated early syphilis (Coöperative Clinical Group) with 145 cases of untreated early syphilis (Bruusgaard series) observed from 3 to 10 and 10 to 20 years.

2. Clinical neurosyphilis is from 2 to 4 times as frequent in the untreated as in the treated cases.

3. The frequency of bone and skin lesions in untreated cases is 17 to 26 times as great as in treated cases.

4. Treatment renders 77% to 63% of patients symptom-free and Wassermann-negative in the 3- to 20-year observation period, as compared with 24% to 36% without treatment.

5. Even seronegative treated patients will present 1.5% to 1.2% abnormal spinal fluids after 3 to 20 years.

6. Adequate treatment by an effective technique gives 96% symptom-free patients with positive or negative blood tests after 3 to 10 years, while *no* treatment gives 61%.

7. In the 10- to 20-year observation period, the same treatment gives 74%; no treatment, 50%.

8. Complications develop largely in irregularly treated patients. The proportion of abnormal spinal fluids in such patients, otherwise negative, may reach 4.5% in the 3- to 10-year period.

9. The cardiovascular results are interpreted.

10. While the relative benignity of many aspects of untreated syphilis is conceded, the results summarized in Items 4 and 6 fully justify adequate and systematic modern treatment for early syphilis.

THE RELATIONSHIP BETWEEN ANTISYPHILITIC TREATMENT AND TOXIC CIRRHOSIS.*

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Is it possible that antisyphilitic treatment consisting of mercury and arsphenamin may produce toxic cirrhosis? If toxic cirrhosis follows antisyphilitic treatment is this possible in a liver not previously damaged by syphilis?

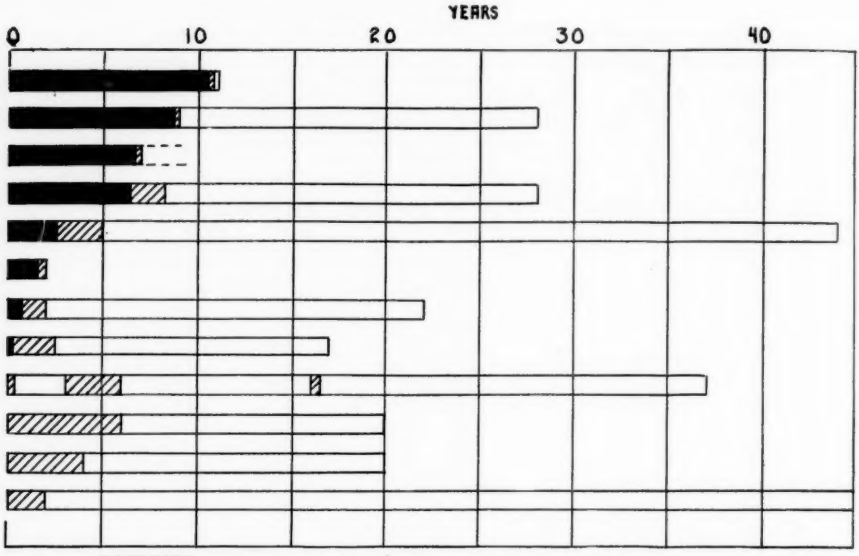
Excluded from consideration here are the established ill effects of antisyphilitic treatment upon the liver such as that described by Wile[1] as a "therapeutic paradox" and severe acute yellow atrophy even though it be called "acute cirrhosis."[2]

In 1929 O'Leary, Green and Rowntree[3] reported 1 case which they called "treatment cirrhosis." This case was that of a man with a mildly positive Wassermann reaction on one occasion who, according to the authors was probably non-syphilitic, but who received 7.9 gm. of arsphenamin, 36 injections of mercury and 200 innunctions of mercury over a period of 5 years. The patient took an unknown amount of treatment from other physicians during the succeeding 5 years. Ten years after the beginning of treatment the patient returned to The Mayo Clinic with ascites and a few months later died of a ruptured esophageal varix. There was no history of alcoholism. The liver was cirrhotic and was reduced in size. In later publications O'Leary[4,5] mentioned the danger of producing cirrhosis of the liver by the administration of arsphenamin, but did not make clear whether or not he felt that this was possible in the absence of hepatic syphilis. Hutchinson,[6] Hamburger,[7] Stockman,[8] and O'Leary, Snell and Bannick[9] have reported cases in which cirrhosis or at least portal obstruction has been attributed to the long continued use of inorganic arsenic. Moreover, the "epidemic" of cirrhosis which occurred in England during 1900 and 1901 was attributed to arsenic in beer.[10,11] Sollmann[12] in his textbook makes the statement that liver degeneration is more marked after inorganic than after organic arsenic compounds.

O'Leary and his coauthors have been vague in dealing with the etiologic relationship of antisyphilitic treatment to cirrhosis but this vagueness has been invoked advisedly. When cirrhosis follows treatment in a syphilitic subject, it is obviously difficult or impossible to be sure that the liver had not been damaged to some extent by syphilis before treatment was begun. Probably all syphil-

* Presented before the Sixth Annual Meeting of the Central Society for Clinical Research, Chicago, October 27, 1933.

ologists admit that vigorous treatment with arsphenamin may cause an increase in the portal obstruction in cases of hepar lobatum. Sudden increase in scar formation without actual damage to liver cells might account for this. That the long continued use of Fowler's solution occasionally results in cirrhosis or that arsenic mixed with beer contributed to the production of cirrhosis in the cases reported from England is generally admitted. That arsphenamin preparations can produce acute necrosis of liver cells seems to be established although many ingenious explanations for postarsphenamin jaundice have been advanced.[13]



Duration of syphilis before treatment was begun.

Duration of arsphenamin treatment.

Interval between last arsphenamin treatment and manifestations of cirrhosis.

CHART I.

In going over the records of patients admitted to the University Hospital since 1921, with conditions resembling cirrhosis, many cases were unsatisfactory for a study such as this. Twenty-one cases of Banti's syndrome, 2 of Felty's syndrome, 8 of Pick's syndrome, 5 of hemochromatosis, and 3 of cinchophen poisoning were excluded. Furthermore, all patients with enlarged livers were excluded, not because it was completely justifiable, but because in this particular study interstitial syphilis of the liver could not be completely ruled out in such cases except by necropsy.

In 20 of our cases of syphilis of the liver the process was not extensive enough to produce portal obstruction. All of these patients

received mercury by innunction and potassium iodid and 9 were treated with arsphenamin. Of the 9 who received arsphenamin 2 developed jaundice after treatment, and in 1 there was also transitory ascites. Most of these 20 patients improved a great deal under treatment.

In 14 other cases the hepatic syphilis was extensive, the spleen was enlarged, and there was portal obstruction. Three of these patients had received arsphenamin before they came to the hospital and 1 was given arsphenamin cautiously while in the hospital. In all 4 the portal obstruction increased after arsphenamin treatment (a therapeutic paradox). Most of the other 10 patients improved under treatment with potassium iodid and mercury or bismuth. One case was much benefited by a splenectomy, after which arsphenamin treatment did not cause ascites. The above 34 cases of hepatic syphilis were excluded from consideration in this study. After eliminating all of the above, as well as all non-fatal cases of probable portal cirrhosis which did not require repeated paracentesis, and all cases complicated by cardiac decompensation, there were only 36 cases remaining in the series.

Of these 36 cases 15 had syphilis. This incidence of syphilis among patients with portal cirrhosis is higher than that found by Symmers[14] in New York and lower than that observed by DeDuc[15] at Ann Arbor. At least 11 of the 15 patients with syphilis received antisyphilitic treatment before cirrhosis became manifest and 1 non-syphilitic patient also received antisyphilitic treatment. The duration of the syphilitic infection, the amount and the nature of treatment, and the relation of these to the onset of cirrhosis is indicated in the chart and table.

It is to be noted that in one-third of our patients in whom a definite diagnosis of portal cirrhosis could be made, there was a history of antisyphilitic treatment preceding the clinical evidence of cirrhosis. Vices are prone to be multiple, so that alcoholism, syphilis and antisyphilitic treatment often coexist in the history of patients with cirrhosis of the liver. In the presence of multiple factors which may bear on the etiology of disease, the clinician usually looks to the pathologist for a decision, but in this instance an authorative opinion can be rendered only by the most experienced pathologist. The cases in this series present several circumstances which tend to incriminate antisyphilitic treatment in the causation of cirrhosis of the liver.

Three of the patients in whom cirrhosis followed antisyphilitic treatment were women whose denial of alcoholism carried conviction. One man would not admit the use of alcohol while one other stated that he had taken alcohol in small amounts but had been an almost total abstainer for a period of 14 years before cirrhosis was recognized. Snell[16] states that cirrhosis usually does not progress except during the period of exposure to the injurious agent. If we

admit the validity of Snell's statement, then the patient who had abstained from alcohol for 14 years might be classed with the 4 who never used alcohol. Four other patients used alcohol occasionally and moderately, but 3 drank to excess for many years. While the incidence of portal cirrhosis is not very high, even in confirmed alcoholics, the possibility of this type of liver damage must be admitted in at least 3 of these 12 cases.

In 7 of the cases the Wassermann reaction was completely negative when cirrhosis developed, and in 3 others the alcoholic antigen gave negative reactions. In only 2 did the Wassermann reaction remain strongly positive. The fact that most of the patients had vigorous treatment and developed cirrhosis at a time when the Wassermann reaction was negative, speaks against the probability of the liver damage being dependent upon the syphilitic infection. The variable duration of the syphilis before cirrhosis appeared and the fact that 1 patient never had syphilis, are other points against the theory that the cirrhosis in these patients may have been due to syphilis.

TABLE 1.

Case.	Age.	Sex.	Alcohol.	Arsphenamin injections.	Mercury.	Wassermann reactions.†			
						Before treatment.		After treatment.	
						Alc.	Chol.	Alc.	Chol.
1	41	M	++++	6	Moderate amount	4+	4+	0	4+
2	54	M	+*	5	Little	?	?	0	0
3	56	M	++	10	Moderate amount	4+	4+	4+	4+
4	46	F	0	27	Much	4+	4+	0	0
5	65	M	++++	36	Much	4+	4+	0	3+
6	54	F	0	?	Too much	0	0	0	0
7	40	M	0	42	Much	4+	4+	3+	4+
8	44	F	0	12	Much	4+	4+	0	0
9	62	M	++	37	Much	4+	...	0	0
10	35	M	++	23	Much	4+	4+	0	0
11	39	M	++	18	Much	4+	4+	0	4+
12	76	M	+++	?	?	4+	4+	0	0

* Used practically no alcohol for 14 years before cirrhosis appeared.

† The Wassermann technique included fixation in the icebox for 4 hours and antigens as indicated.

Undoubted signs of cirrhosis appeared in 6 of the cases within 8 months or less after combined treatment with mercury and arsphenamin. In Case 9 ascites developed after intensive antisyphilitic treatment and a subsequent injection of arsphenamin was followed by an increase in the amount of ascites. Treatment was then stopped after which the signs of portal obstruction disappeared and the patient has remained free from ascites for 3 years. The ascites also increased in Case 11 under arsphenamin treatment.

In two instances there were signs of arsenic poisoning evidenced by peripheral neuritis in 1 and arsenical dermatitis in the other. One patient suffered from rather marked mercurial poisoning.

Case 6 is of particular interest in that there was never any evidence of syphilis, even in the necropsy findings. This patient took antisyphilitic treatment at her own insistence and developed mercury poisoning in 1923. We were unable to determine the extent of the arsphenamin treatment. In 1925 a "hob-nail liver" was discovered at operation and in 1927 she developed ascites and died. In this case syphilis and alcohol can be definitely excluded.

All of the 12 patients considered here received both arsphenamin and mercury. Strathy, Smith and Hannah[17] have suggested that the kidney damage occasioned by mercury might be a predisposing factor in the toxic effects of arsphenamin. In no case was there a history of postarsphenamin jaundice and no symptom which would suggest a non-fatal acute yellow atrophy of the liver was observed while the patients were under treatment. Seven of the patients received part or all of their treatment at the University Hospital.

Necropsies were obtained in 16 of our 36 cases of atrophic cirrhosis. Among the 16 cases in which necropsy studies were made there were 4 syphilitic subjects. Three of these had received antisyphilitic treatment. A necropsy was also obtained in the 1 patient (Case 6) who was non-syphilitic but who had received antisyphilitic treatment. Sections of the livers from all 16 cases were submitted to Dr. F. B. Mallory for an opinion.

The sections submitted included one from the liver of a man who had had untreated syphilis for 40 years, but who was also a confirmed alcoholic. Dr. Mallory commented on the section as follows: "Old alcoholic. Slight hyalin present."

In Case 11 there was a history of moderate alcoholism (wine) and the outstanding feature in addition to cirrhosis was polycythemia with cyanotic and painful extremities. The patient was syphilitic and received 18 injections of neoarsphenamin. A small amount of ascites existed at the beginning of the last course of 6 injections, but the fluid in the abdomen increased rapidly during and after these treatments. Dr. Mallory considered that the cirrhosis in this case was probably on an alcoholic basis but he could find no hyalin.

In Cases 6, 8 and 10 Dr. Mallory believed the cirrhosis to be the result of a previous acute yellow atrophy (toxic cirrhosis[18]).

There is every reason to expect toxic cirrhosis as one of the complications of antisyphilitic treatment. Any toxic principle which is capable of producing acute yellow atrophy may also produce toxic cirrhosis. The fact that cirrhosis followed antisyphilitic treatment in 2 non-syphilitic subjects is strong evidence that such treatment can produce this liver lesion alone without the predisposing influence of hepatic syphilis. In our non-syphilitic patient (Case 6) the cirrhosis was of the toxic type and the gross description of the liver

in the case of "treatment cirrhosis" reported by O'Leary, Green and Rowntree is also compatible with a diagnosis of toxic cirrhosis. The histologic changes in the livers of the syphilitic cases, 8 and 10, were the same as those in the non-syphilitic subject (Case 6).

The author does not wish to imply that toxic cirrhosis is a hazard of major importance in the treatment of syphilis with arsphenamin. However, the evidence would seem to substantiate the claim that toxic cirrhosis of the liver may result from antisyphilitic treatment *per se*. In Iowa, cirrhosis of the liver is not common but a surprising number of the patients seen here with cirrhosis of the liver have had antisyphilitic treatment (at least 12 out of 36).

All of the 12 patients in this series, in whom cirrhosis followed antisyphilitic treatment, received arsphenamin or neoarsphenamin or both between 1917 and 1926. This is in keeping with Dr. Mallory's observation that liver damage following arsphenamin was more common for a few years after the introduction of American-made drugs than it was either before or since.

Summary. Twelve patients are reported in whom cirrhosis of the liver with portal obstruction followed antisyphilitic treatment with arsphenamin and mercury. Clinical evidence of disease of the liver was not found in any case before antisyphilitic treatment was begun.

In 3 of the 4 patients who came to necropsy the cirrhosis was of the toxic type, *i. e.*, the result of a previous acute yellow atrophy.

The author wishes to express his appreciation for the help given by Drs. F. B. Mallory, F. Parker, Jr., and P. A. O'Leary.

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RECURRENT LARYNGEAL PARALYSIS IN LEFT VENTRICULAR FAILURE.*

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The occurrence of left recurrent laryngeal palsy in exceptional instances of mitral stenosis is well known. So far as we have been able to find, this palsy has not been described as a manifestation of any other intrinsic disease of the heart, although it may be produced by aneurysm or diffuse dilatation of the aorta and very rarely by pericardial disease.

Recently, we have observed the development of left recurrent laryngeal paralysis in 3 instances of the arteriosclerotic type of heart disease with failure of the left ventricle. In 2 of the cases there was coronary thrombosis, while the third had left ventricular failure, due to chronic glomerulonephritis and coronary arteriosclerosis. The cases seem worthy of description not only because recurrent laryngeal paralysis has not been reported as a complication of coronary thrombosis or other forms of left ventricular failure, but also because they seem to throw light on the pathogenesis of the same palsy in mitral stenosis.

Report of Cases. Case 1.—A woman, aged 57, was admitted because of precordial pain and dyspnea. For several years she had had occasional aches in the precordial region. Two weeks before admission she was awakened from sleep by agonizing substernal pain. This persisted for almost 12 hours, when it was relieved by a hypodermic injection. The pain was accompanied by orthopnea, profuse perspiration and fever. *The day after the attack she became hoarse and remained so.* The day before admission she had another, almost identical, episode of precordial pain.

On physical examination, the patient was seen to be orthopneic. The lips and nail beds were cyanotic. The temperature was 99° F., the heart rate 100. Presystolic gallop rhythm was audible inside the apex and the second sound was louder at the pulmonic than at the aortic area. Blood pressure was 120/80 mm. The edge of the liver was felt 4 cm. below the costal margin. There was marked edema about the ankles. *Laryngoscopic examination revealed complete paralysis of the left vocal cord, which was in the cadaveric position.*

* Aided by a grant to The Emanuel Libman Fellowship Fund in memory of Adele Schiff.

The teleoroentgenogram (Fig. 1) revealed marked enlargement of the heart to the left. The vascular shadows extending from either hilum were markedly accentuated and broadened. Both lung fields exhibited coarse mottling, diminishing from hilum to periphery, due to intense engorgement and distention of the pulmonary vessels. The electrocardiogram showed left axis deviation. T_2 and T_3 were inverted.

The patient was given an injection of merbaphen, which produced copious diuresis. With this, the edema disappeared and the liver became impalpable. At this time, the venous pressure was found by direct measurement to be 8 cm. of water, a normal value. The evidences of intense pulmonary engorgement persisted. From the point of view of circulatory dynamics, therefore, the patient was suffering, at this time, from left ventricular failure, a disturbance characterized by engorgement of the pulmonary circuit accompanied by normal systemic venous pressure.

The patient's condition became steadily worse. Toward the end there were added to the manifestations of insufficiency of the left heart such evidences of right ventricular failure as rise in venous pressure to 12 cm., dependent edema, bilateral pleural effusions and enlargement of the liver. The electrocardiogram changed to that of the common type of bundle-branch block. The left recurrent laryngeal paralysis persisted. Pulmonary edema developed and the patient succumbed 7 weeks after admission.

Necropsy was performed 5 hours after death. The larynx showed no changes.

The *mediastinum* was carefully dissected. No neoplasm, mediastinitis or lymphadenopathy was found. The left vagus nerve was traced and the recurrent branch followed from its origin to the larynx. About 3 cm. from its origin a segment of the left recurrent laryngeal nerve, about 0.5 cm. in length, was definitely constricted and exhibited bluish discoloration. The constricted and discolored portion of the nerve was that which lay between the arch of the aorta above and the left pulmonary artery below, and abutted against the obliterated ductus arteriosus medially. Proximally and distally to this area, the nerve showed no gross changes.

The *heart* was enlarged. There was moderate hypertrophy and dilatation of both ventricles; the auricles were also dilated, the right more than the left. A circular area, about 1 inch in diameter, on the anterior surface of the left ventricle above the apex was purplish-red in color, dimpled when unsupported and felt soft (microscopically, there was degeneration of the muscle fibers in this area with which was intermingled young connective tissue). The myocardium of the lower two-thirds of the interventricular septum and the anterior and apical portion of the left ventricle showed fibrosis. The mitral and other valves were negative. There was severe arteriosclerosis of both coronaries. In the anterior descending branch of the left coronary artery was a grayish-brown thrombus which completely obliterated the lumen and extended distally about 3 cm. There was an organized thrombus in the right coronary artery about 1 cm. from its origin.

The pulmonary artery and its branches exhibited discrete atheromatous plaques. They were hardly, if at all, dilated, the root of the pulmonary artery measuring 8.5 cm. in circumference. There were adherent thrombi in some of the branches of the pulmonary artery.

Both pleural cavities contained clear fluid. The lungs were markedly engorged and edematous. The cut surface had a rusty tint and there was an infarct in either lower lobe.

The liver extended about 5 cm. below the costal margin, was firm, brownish-red in color and considerably engorged.

Dr. J. H. Globus was kind enough to examine the left vagus and recurrent laryngeal nerves, with the following results:

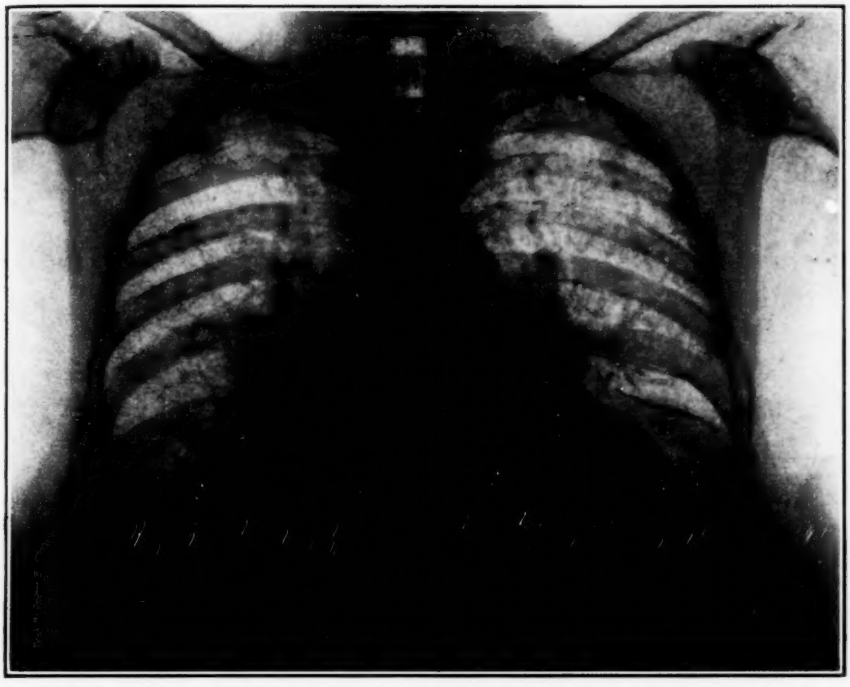

FIG. 1.—Teleoroentgenogram of Case 1. Intense pulmonary engorgement. Note especially the thick and dense shadows cast by the distended primary and secondary branches of the pulmonary artery.

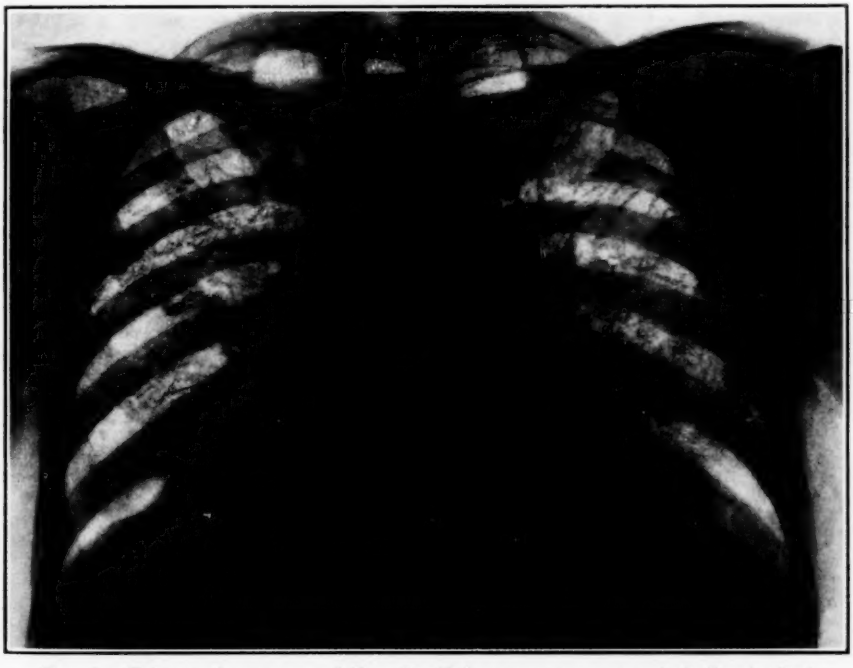

FIG. 2.—Teleoroentgenogram of Case 3. Pulmonary engorgement similar to that in Fig. 1.

Section A—left vagus nerve proximal to the origin of the left recurrent laryngeal nerve: Marchi preparation showed quite marked and diffuse myelin degeneration.

Section B—left recurrent nerve at the point where it passes under the aortic arch and above the left branch of the pulmonary artery: Marchi preparation showed fairly marked degeneration, approximately as at *A*.

Sections C and D—left recurrent laryngeal nerve distal to B: Marchi preparation showed occasional small deposits of fat with grayish discoloration of some myelin rings.

Section E—left recurrent laryngeal nerve, 1 cm. distal to D: Marchi preparation displayed a larger number of fat deposits, some of which showed loss of ring outline and assumed the character of plaques.

Weigert preparations revealed few definite changes, possibly because the degenerative process was not sufficiently massive to be revealed by this method.

Comment on the Histologic Findings. The Marchi preparations indicate fairly marked degeneration of the left recurrent nerve at the point of most probable compression and distally. It is, however, difficult to explain the more marked degeneration in the segment taken from the vagus trunk unless it is assumed that afferent fibers coursing from the recurrent laryngeal nerve upward in the vagus have also been affected by the compression and have undergone degenerative changes.

CASE 2.—A man,* aged 36, was admitted complaining of precordial pain, orthopnea and cough. Three years previously he had been found to have a systolic blood pressure of 200 mm. He felt well until 1 year before admission, when he began to have attacks of precordial pain. These pains recurred frequently and were often incited by exertion. Three weeks before admission, while driving an automobile, he began to cough up large volumes of pink, frothy fluid; at the same time he had viselike precordial pain radiating down the left arm. A week later he had a similar attack following coitus. Ten hours before entering the hospital he had a third attack of pulmonary edema accompanied by precordial pain.

On admission, the patient was coughing up frothy, bloody sputum. The heart was enlarged to the left. The rate was rapid and presystolic gallop rhythm was heard. Moist râles were audible in both lower lobes. The liver edge was 2 cm. below the costal margin. Arterial pressure was 120/102 mm., then falling to 106/80 mm. Venous pressure was 6.5 cm. The electrocardiogram was definitely indicative of recent infarction in the posterior portion of the left ventricle in the part usually supplied by the right coronary artery. There was nodal rhythm with a rate of 115. The *R–T* interval was elevated in the second and third leads. *T* was inverted in the second and third leads and there was a large *Q* wave in the third lead.

Five days after admission, Dr. Rabinowitz noted that *the patient was hoarse.* The hoarseness persisted to the end. Two laryngoscopic examinations at an interval of a week revealed *left abductor paralysis.* Fifteen days after admission the patient suddenly succumbed. Necropsy was not permitted.

CASE 3.—A conductor, aged 33, was admitted to The Mount Sinai Hospital 3 times in the last year of his life. On the first admission he complained of headache and vomiting. He was found to have blood pressure of 232/144 mm., hypertensive neuroretinopathy and marked albuminuria. His symptoms improved and he was discharged. He was admitted again 3 months later for the same symptoms, as well as blurring of vision. This stay lasted 6 weeks.

* This patient was in The Jewish Hospital of Brooklyn, under the care of Dr. M. A. Rabinowitz, to whom we are greatly indebted for his courtesy in allowing us to report the case.

Six months later he was admitted for the third time. Fifteen days before he had noted dyspnea, which soon developed into severe orthopnea. On physical examination, there was slight puffiness of the ankles. The heart was enlarged to the left, the rate was rapid and gallop rhythm was present. Medium-sized moist râles were audible over both lower lobes. The liver was not palpable but percussion indicated slight enlargement. Arterial pressure was 210/150 mm. Venous pressure was 8.5 cm. Roentgenographic examination revealed intense engorgement and distention of the pulmonary vessels (Fig. 2). The non-protein nitrogen of the blood was 86 mg. %.

Three days after admission it was noted that *the patient was hoarse and laryngoscopic examination revealed left abductor paralysis.* This persisted until the death of the patient.

Two weeks after admission a pericardial friction rub was heard. Other manifestations of uremia appeared and the patient succumbed about 6 weeks after admission.

Necropsy. The cut surfaces of the *lungs* were very wet and abundant frothy fluid exuded from the bronchi. The main branches of the pulmonary artery were somewhat dilated and the walls were slightly thickened.

Heart: the *pericardial cavity* contained about 5 ounces of serosanguineous fluid. Both the visceral and parietal layers of the pericardium were studded with plaques of fibrin. The right ventricle was slightly hypertrophied and dilated; the left markedly hypertrophied and dilated. The mitral and other valves showed no changes. The coronary arteries were moderately sclerotic without being narrowed.

The *kidneys* were granular, and microscopic examination revealed glomerulonephritis of long standing.

The *left vagus and recurrent laryngeal nerves* were followed. The latter was flattened where it passed between the arch of the aorta and the left pulmonary artery. We are indebted to Dr. J. H. Globus for the following results of the microscopic examination:

Left vagus nerve proximal to the origin of the recurrent laryngeal nerve: Paraffin sections stained with hematoxylin and eosin showed no significant changes. Celloidin sections stained by the Marchi method failed to reveal myelin degeneration. Frozen section stained with Sudan III and hematoxylin showed fat in the connective tissue about the nerve but no fat droplet replacement of myelin within the nerve trunk. In the perineural tissues several medium-sized arteries were atherosclerotic.

Left recurrent laryngeal nerve where it passes between the arch of the aorta and the left pulmonary artery: Paraffin sections stained with hematoxylin and eosin were negative, as was the Marchi section. Frozen sections stained with Sudan III and hematoxylin showed fat droplets in ring formation about a few intact axis cylinders.

Left recurrent laryngeal nerve distal to the preceding: Paraffin sections stained with hematoxylin and eosin showed areas of vacuolization of myelin. Sections stained by the Marchi method revealed definite myelin degeneration with fat droplet replacement. Frozen sections stained with Sudan III and hematoxylin confirmed the finding by the Marchi method; fat droplets were seen surrounding many axis cylinders.

Left vagus nerve distal to the origin of the recurrent laryngeal nerve: Paraffin sections stained with hematoxylin and eosin, Marchi sections and frozen sections stained with Sudan III and hematoxylin did not show significant changes.

Sections from the above locations stained by the Weigert method revealed no changes sufficient to warrant deductions.

Summary of the Histologic Findings. The maximum degenerative change, as evidenced by myelin degeneration and fat droplet replacement is present

in the section taken from the left recurrent laryngeal nerve distal to the point where it passes between the left branch of the pulmonary artery and the arch of the aorta. The vagus nerve shows no significant changes.

Discussion. In each of the 3 cases described, the development of left ventricular failure, due to hypertensive and arteriosclerotic heart disease, was followed by paralysis of the left recurrent laryngeal nerve. This sequence of events suggests that the damage to the nerve is a result of the left ventricular failure, a conception which is fortified by the absence in the 2 cases that came to necropsy of any other cause for recurrent laryngeal palsy.

The mechanism by which injury to the left recurrent laryngeal nerve results from left ventricular failure can, perhaps, be most readily elucidated in the light of what is known about the pathogenesis of the same paralysis in mitral stenosis. By investigations on thoraces hardened *in situ* and *in toto*, Fetterolf and Norris[1] have shown that left recurrent laryngeal palsy in mitral stenosis is due to compression of the nerve between the left pulmonary artery and the aorta or ductus arteriosus. The left recurrent nerve passes between the arch of the aorta and the left pulmonary artery in a situation in which the two vessels are very close to one another (4 mm. apart, according to Fetterolf and Norris); indeed, the nerve is even normally flattened as it hooks around the aorta. It is quite obvious that even comparatively slight dilatation of the pulmonary artery might readily result in compression of the nerve between the pulmonary artery and the aorta, both of which are comparatively firm structures in consequence of the blood-pressure within them. Of course, a prerequisite for such compression is that the nerve be so fixed that it cannot merely be displaced laterally as the pulmonary artery dilates. The ductus arteriosus probably plays an important part in producing the palsy in this very way, namely, by preventing displacement of the nerve to the right. As a result, the nerve is constricted in a triangle bounded by the arch of the aorta, the left pulmonary artery and the ductus arteriosus. Apparently, however, the anatomic conditions necessary for the compression of the nerve by the expansion of the pulmonary artery are fulfilled in only a small proportion of individuals, for recurrent laryngeal paralysis is an unusual complication of mitral stenosis.

Previous investigators have visualized the compression of the left recurrent laryngeal nerve in mitral stenosis as due to *anatomic* dilatation of the pulmonary artery. This has, indeed, been present in some of the cases but in others it has been equivocal or absent. However, it does not seem that such anatomic dilatation, which can be demonstrated at necropsy, is necessary for the compression of the nerve. There may very well be a so-called *dynamic* dilatation, due to high pressure within the vessel, and which is not evident at necropsy. How marked such dynamic dilatation of an artery

may be is familiar to clinicians from the fluoroscopic appearance of the aorta in many instances of aortic insufficiency. As a result of the large volume of blood ejected into the aorta by each systole in aortic insufficiency, the aorta may appear greatly dilated during life, but at necropsy its measurements do not exceed the normal. Similarly, roentgenographic examination in mitral stenosis reveals that the pulmonary artery and its first branches are greatly dilated and, as in the instance of aortic insufficiency, this dilatation may be largely or completely "dynamic;" at postmortem, the vessels in question are not correspondingly, if at all, dilated.

In the light of these facts, it seems probable that *functional* moments predominate in the compression of the left recurrent laryngeal nerve in mitral stenosis. As a result of the mitral obstruction, engorgement and hypertension of the lesser circulation develop. One of the consequences of the increased pressure is dynamic dilatation of the pulmonary artery and its branches. The development of the latter is facilitated by the great elasticity of the pulmonary artery and its first branches. It is true that if the hypertension of the pulmonary circulation is sufficiently protracted, arteriosclerosis, diminished elasticity and anatomical dilatation of the pulmonary artery may result. But such anatomical dilatation of the pulmonary artery is not always present when left recurrent laryngeal palsy complicates mitral stenosis.

In the 3 cases described above of left recurrent laryngeal palsy complicating hypertensive and arteriosclerotic heart disease, there is every reason to believe that the functional element of hypertension of the lesser circulation with resultant dynamic dilatation of the pulmonary artery was the cause of the compression of the nerve, just as in mitral stenosis. The evidence for this view is as follows:

1. In all the cases the recurrent laryngeal palsy *followed* the onset of left ventricular failure.

2. In Case 1 the left recurrent laryngeal nerve was definitely constricted and discolored for a length of 0.5 cm., where it passed through the triangle bounded by the arch of the aorta, the left pulmonary artery and the ductus arteriosus. In Case 3 the histologic findings also indicated compression at this point.

3. In Case 1 no significant "anatomic" dilatation of the pulmonary artery was demonstrable at necropsy; the aorta and the ductus arteriosus likewise exhibited no notable changes. In Case 3 the dilatation of the pulmonary artery found at necropsy was but minimal.

4. The evidences of engorgement and hypertension of the pulmonary circuit with dynamic dilatation of the pulmonary artery and its branches during life were clear-cut and unequivocal: (*a*) The pulmonic second sound was louder than the aortic second sound. (*b*) The chest films in Cases 1 and 3 revealed intense engorgement of the pulmonary vessels, the dilatation of the smaller radicles

being visible far out toward the periphery of the lung fields. We did not see the chest film of Case 2. (*c*) In Case 2 there were repeated attacks of massive pulmonary edema, while the other 2 patients had marked pulmonary edema at necropsy.

Summary. Three cases of left recurrent laryngeal palsy complicating hypertensive and arteriosclerotic heart disease with left ventricular failure are described. Two of the cases were instances of coronary thrombosis.

Evidence is presented that the left recurrent laryngeal palsy was due to compression of the nerve between the left pulmonary artery, the arch of the aorta and the ductus arteriosus. The cause of the compression is regarded as dynamic dilatation of the pulmonary artery due to the engorgement of the lesser circuit engendered by the failure of the left ventricle.

In the light of these cases and other evidence, it is suggested that when recurrent laryngeal paralysis complicates mitral stenosis, the *dynamic* dilatation due to the hypertension of the lesser circulation probably plays a significant part.

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LIMITATIONS OF AUSCULTATION FOR THE DIAGNOSIS AND STUDY OF TUBERCULOUS PULMONARY CAVITIES.

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The following observations of the limitations of auscultation were made in connection with a study of the healing of tuberculous pulmonary cavities.[1] The series consisted of 296 cases of pulmonary tuberculosis with cavity and with tubercle bacilli in the sputum; the total number of cavities estimated from roentgenograms was 464. All patients were examined once a month and stereoscopic Roentgen ray films were taken on an average of every 2 months. Correlation was thus possible between stethoscopic findings and Roentgen ray interpretations, both in regard to the presence of cavity signs and alterations in cavity dimensions. Elicitation of any one of the usual textbook physical signs of cavity was sufficient to lead the examiner to suspect its presence, while more than one strengthened the likelihood. Patients with so-called "silent cavities,"

i. e., cavities visualized in the roentgenogram but not suspected on physical examination, were reëxamined to make certain that cavity signs were not overlooked. Particular attention was given to the area of distribution and character of râles. Whenever significant changes in the lesion were noticed in the serial Roentgen ray films, correlation was made with the physical examination for that time, especially as to changes in râles.

Cavity was diagnosed by physical examination in 119 (40%) of the 296 cases. This figure refers to cavity-bearing areas, containing either single or multiple cavities. In a separate study of 170 cases with solitary cavity, a diagnosis of cavity was made in only 53 (31%). Here size was a factor, because the percentage of positive diagnoses increased from 21% for cavities of dimensions not over 2 by 2 cm. to 53% for cavities over 4 by 4 cm. It was likewise true that fresh, thin-walled cavities were more easily missed than those with fibrous walls or surrounding consolidation.

To determine how accurately changes in râles indicated mutations in pathologic anatomy as portrayed by Roentgen ray, two large contrasting groups of the original study[1] were examined. The first group comprised 65 cases that secured spontaneous closure of cavity, the criteria for which were the disappearance of shadows representing cavity in serial Roentgen rays and the absence of tubercle bacilli from the previously positive sputum for at least 3 consecutive months. The second group comprised 84 cases in which the size of the cavities at the end of treatment was the same or larger.

Of the group that secured spontaneous closure of cavity, râles were unaltered after closure in 30.8%, diminished in 67.7% and increased in 1.5%. Of the second group, finally classified as unimproved, râles were increased in 40.4%, unchanged in 47.6% and diminished in 11.9%. Consequently, estimation of changes in cavities deduced from variations in râles is unreliable, since râles may increase or remain the same while the lesion heals, or they may diminish while the lesion is stationary or progressive.

While this experience demonstrates that auscultation has its limitations in the diagnosis of pulmonary cavities and in the detection of changes during healing or enlargement, it must not be assumed that Roentgen ray interpretation is infallible. Many intrapulmonary lesions cast shadows on the roentgenogram indistinguishable from tuberculosis and small tuberculous lesions cannot be clearly shown, especially if Roentgen ray technique is not the best. Furthermore, such conditions as pleural friction, pulmonary edema, bronchitis, and sometimes emphysema can be more readily detected by auscultation than by Roentgen ray. Treating tuberculosis on the basis of Roentgen ray alone overlooks the importance of other clinical features and of personality as a guide to treatment

and prognosis. For this purpose a well-taken history and a careful physical examination are indispensable.

Summary and Conclusions. If reliance had been placed on auscultation alone in this series of 296 cases of cavitary tuberculosis, only half the large cavities diagnosable by Roentgen ray would have been detected and 4 out of 5 of the smaller ones would have been missed. In practice, it is therefore wise to withhold final opinion on the presence or size of cavity until the Roentgen film has been read. Roentgenograms and fluoroscopic examinations at intervals of weeks or months are the best means at our command of observing the behavior of cavities as to size and character. For this purpose deductions made from changes in extent, character, and number of râles are unreliable, since râles may increase or remain the same as the disease heals or they may diminish as the disease grows worse.

Recognition of these limitations of auscultation leads to greater accuracy in diagnosis and emphasizes the need for correlation of physical, Roentgen ray and laboratory examinations.

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SOME EFFECTS OF QUININ DERIVATIVES IN EXPERIMENTAL PNEUMOCOCCUS STUDIES.*

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In this article we are reporting the results of a study of certain quinin derivatives with reference to their power to destroy the pneumococcus in the test tube and to protect mice which have been

* Read at the meeting of the Association of American Physicians at Atlantic City, May 1, 1934.

inoculated by an intraperitoneal injection of pneumococci.* The clinical results in a few cases which we have treated with the ethylapoquinin made at the Mellon Institute have been very satisfactory, but a much larger series of cases must be studied as a basis for conclusions. Type II pneumococcus was used, although we have made observations, as have others, to indicate that all pneumococci are affected equally by the quinin derivatives. Also, the toxicity of the derivatives was estimated by intraperitoneal injection in mice. We have examined 35 different preparations of the quinin group (21 various salts as given below, 12 different preparations of ethylapoquinin and 1 each of hydroxyethylapoquinin and hydroxyethylhydrocuprein); of these we have excluded, as being of little value for their slight antipneumococcic power, all but 3. The 3 which we have studied in detail are ethylapoquinin, hydroxyethylapoquinin and hydroxyethylhydrocuprein. Ethylhydrocuprein (optochin) was used in practically all of our experiments at the same time, naturally as a control quinin derivative of which the action on the pneumococcus and the toxicity are well known.

Ethylapoquinin was discovered, in 1895, in Germany, by Lippmann and Fleissner.[1] In 1930, Miura and Okamoto,[2] in Japan, noted that it had greater bacteriocidal power for the pneumococcus in the test tube, gave more protection to mice inoculated with pneumococcus and was less toxic than optochin. In the following year, Miura and Sogen,[3] and Okamoto[4] confirmed this work. In 1931, Osato and Watanabe[5] reported some observations on 10 cases of influenzal pneumonia—the only clinical report on the use of ethylapoquinin of which we are aware. The authors were impressed with the results noted in the small group of cases. Two of the patients died, but 1 was apparently a terminal case at the onset of the treatment. The dosage was 1.5 gm. of the base or 1 gm. of the hydrochlorid in divided doses for the 24-hour period. It was continued for 3 or 4 days. One fatal case was given, 7.5 gm. in 5 days. One of the patients had a transitory blindness for a few days. From reading this report, one cannot really estimate the severity of the infection of the cases, for no observations were made as to the presence of pneumococci in the blood stream as indicated by positive blood cultures. The dosage of the drug was the same as has been recommended for optochin and it is of interest that one example of visual disturbance was noted. In 1933, Gundel and Seitz,[6] in Germany, confirmed the findings of Miura and Okamoto.

Hydroxyethylapoquinin and hydroxyethylhydrocuprein are new derivatives made at the Mellon Institute.

* In this work we were associated with Drs. L. H. Cretcher, C. L. Butler and A. G. Renfrew, of the Department of Research in Pure Chemistry of the Mellon Institute. They will make a separate report on the chemical phases of the preparations. We wish to thank also Prof. W. T. Dawson, of the University of Texas, for assistance.

The bacteriocidal action of the various quinin derivatives on the pneumococcus was carried out in the following way: 0.1 cc. of a 1 to 1000 dilution of an 18-hour broth culture was added to a dextrose broth which contained the quinin derivative in the proper dilution. At the end of 2, 4, 6, 10 and 24 hours, blood-agar plates were streaked with a standard loop from the broth and the colonies of pneumococci were counted in 24 hours. It is well known that the quinin derivatives vary greatly in their bacteriocidal action on the pneumococcus *in vitro*. We used optochin as the control drug, and only those preparations which equalled optochin in their bacteriocidal power were further studied, except in 1 instance, hydroxyethylhydrocuprein, which was definitely lower. The *in vitro* tests, therefore, were used more to exclude the weaker preparations in antipneumococci power than to attempt to accurately define the maximum bacteriocidal dilutions of each derivative. Chart I gives the end results of this part of our work. Any one of several specimens of ethylapoquinin showed the same bacteriocidal effect in the dilution stated. Chart II shows a fairly typical curve of the bacterial count for one of the ethylapoquinins and hydroxyethylhydrocuprein. Fresh solutions of the quinin derivatives were always used as the bacteriocidal power for pneumococcus is lowered if the diluted solutions are allowed to stand for a few days.

The other quinin derivatives, which we have tested and discarded on account of their lesser bacteriocidal power for the pneumococcus, were as follows:

1. Quinin sulphate (neutral)
2. Quinidin sulphate (neutral)
3. Cinchonin sulphate (neutral)
4. Cinchonidin hydrochlorid (neutral)
5. Epiquinin dihydrochlorid
6. Epiquinidin dihydrochlorid
8. Hydroquinin neutral sulphate
9. Quitenin hydrochlorid
10. Ethylquitenin hydrochlorid
11. Quitenidin
12. Hydroquininon hydrochlorid
13. Hydroquinin neutral sulphate
13. a. Hydroquinin dihydrochlorid
14. Epihydroquinidin dihydrochlorid
16. Hydroxydihydroquinin dihydrochlorid
19. Isoquinin dihydrochlorid (?)
20. Cl-ethylhydrocuprein dihydrochlorid
28. Niquin dihydrochlorid
29. Ethylcuprein dihydrochlorid
33. Vinylhydrocuprein dihydrochlorid
34. Ethoxyethyl hydrocuprein dihydrochlorid

CHART I.—PNEUMOCOCCIDAL POWER IN VITRO.

Drug.	No.	Killed pneumococci in
Ethylhydrocuprein . . .	0	1 to 800,000 dil.
Hydroxyethylhydrocuprein .	7	1 to 200,000 "
Ethylapoquinin	15, 22, 23, 26, 31, 32	1 to 800,000 "
Hydroxyethylapoquinin . .	30	1 to 800,000 "

The estimation of the toxicity of the quinin derivative was carried out on mice by injection intraperitoneally of doses, ranging from 2 to 7 mg. If death occurred, it almost invariably happened in from 5 to 30 minutes. Animals surviving $\frac{3}{4}$ hour practically always lived. The toxicity experiments were also used as a method to eliminate some of the preparations, as it was useless to proceed with highly toxic

derivatives. In these experiments we used optochin as a control quinin derivative. Chart III brings out two interesting points in reference to toxicity: (1) There is a considerable variation in the different preparations of ethylapoquinin. We have been able to compare samples made in Japan, in Germany and at the Mellon Institute. (2) All of the preparations of ethylapoquinin which we have examined showing a levorotatory power of 180 or less were very toxic and as the optical activity rose above −200, toxicity definitely decreased. Cretcher[7] has pointed to this fact as being of great practical value in the preparation of this compound. On the other hand, the actual

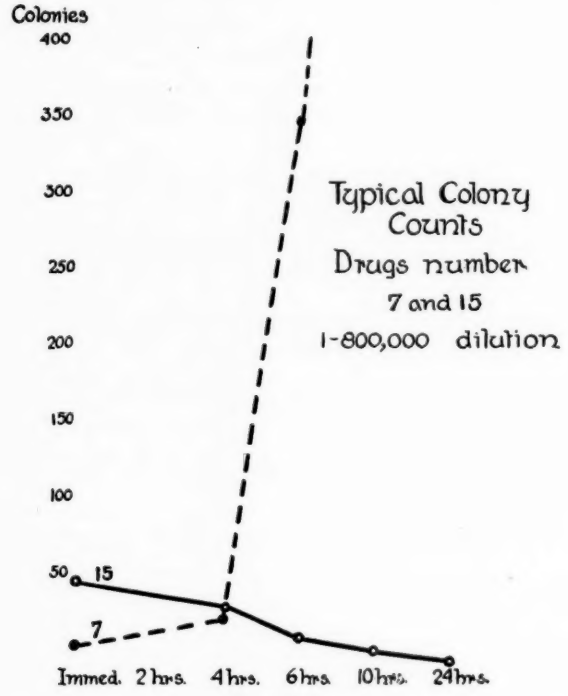

CHART II.

level of the levorotarory power does not necessarily indicate the relative degree of toxicity as Chart III shows in the last two numbers, 15 and 31. This chart also shows in preparations 23 and 26, which represent a fairly pure end product, how earlier fractions of the same preparations varied in their toxicity as noted in 18 and 22 (for end product 23) and 24, 25 and 27 (for end product 26). In Chart III only 10 mice were used for the toxic fractions as indicated in derivatives numbered 18 and 22; in 25, 26 and 27. There is probably an inaccuracy in Chart III which shows 23 at 2 mg. (15 mice) with a higher level of death than 23 at 3 mg. (30 mice). The

error of determination of toxicity is of course less with 30 animals than with 10 or 15 in a group.[8] In all the other columns 30 mice were used.

Chart IV shows the relative toxicity of the quinin derivatives. It is to be noted that the ethylapoquinins vary appreciably. Prepa-

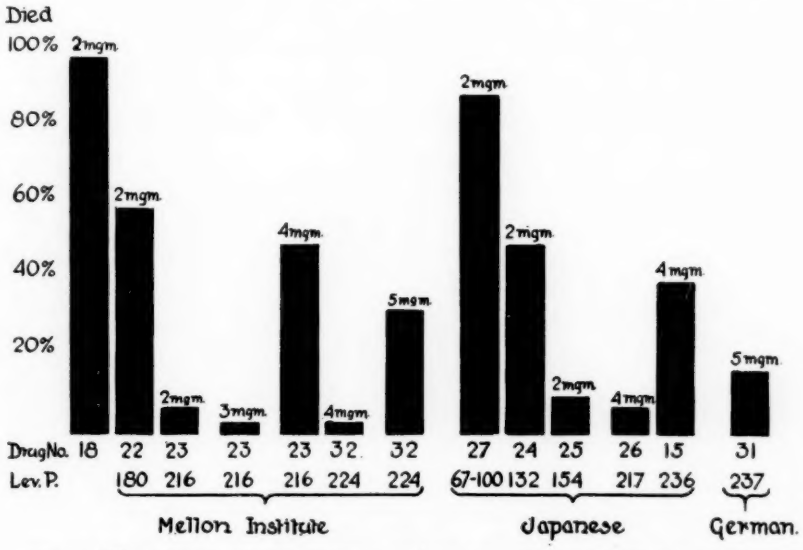

CHART III.—Comparative toxicity of various preparations of ethylapoquinin—dihydrochlorid.

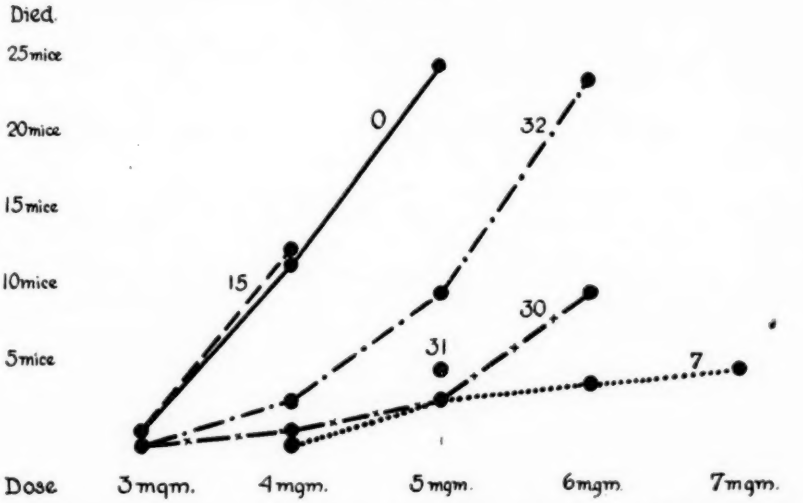

CHART IV.—Comparative toxicity of the hydrochlorids of ethylhydrocuprein (0), hydroxyethylhydrocuprein (7), ethylapoquinin (15), (31), (32), hydroxyethylapoquinin (30).

ration 15 (Japan) is more toxic than 32 (Mellon Institute), while 31 (Germany) is slightly less toxic but also slightly less protective (Chart V) than 32. Of greater interest to us was the curve of hydroxyethylapoquinin, 30. This derivative is less toxic than any ethylapoquinin studied. Finally in hydroxyethylhydrocuprein, 7, we have the least toxic of all derivatives that we have examined.

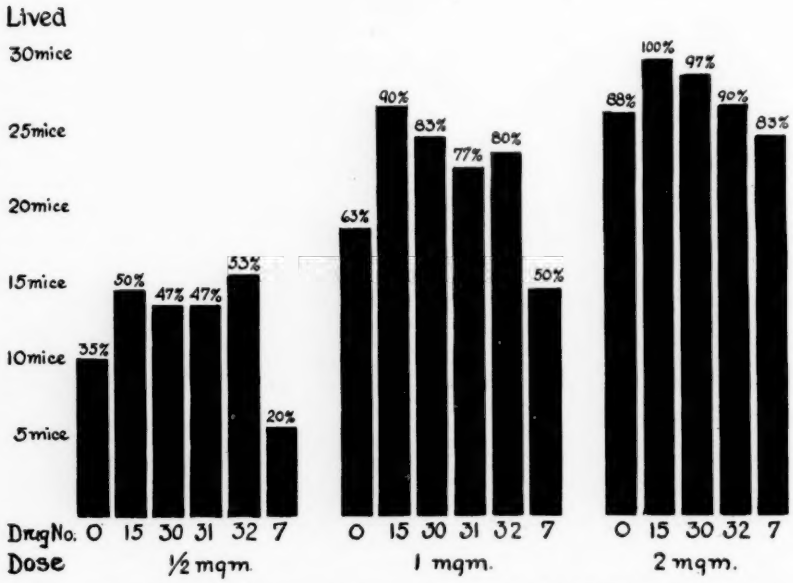

CHART V.—Comparative protective power of the hydrochlorids of ethylhydrocuprein (0), ethylapoquinin (15), (31), (32), hydroxyethylhydrocuprein (7), hydroxyethylapoquinin (30).

The protection of mice against intraperitoneal injections of pneumococci was carried out in the following manner: 0.1 cc. of an 18-hour broth culture of pneumococcus, which in the same quantity in a dilution of 1 to 1000 would kill 20- to 22-gm. mice in from 16 to 20 hours, was injected into the peritoneal cavity. This dose is, therefore, 1000 times the lethal dose. One half hour after the injection, the quinin derivative was given intraperitoneally in 3 different dosages, namely, 0.5 mg., 1 mg. and 2 mg. In each series of protective experiments for each dose 30 mice were used, but as optochin was used as a control drug in all protective tests, except with 31, each dark column for optochin represents 60 mice. Further for each group of 30 mice in all of the protection tests, 6 controls were used, and of this number, 120 in all, only 5 failed to die. Chart V indicates that ethylapoquinin is superior to optochin in protection more definitely noted in the smaller doses, 0.5 and 1 mg.

The different ethylapoquinins also vary a little in their protective power. Hydroxyethylapoquinin appears to be more powerful than ethylapoquinin except 15, which is, however, the most toxic ethylapoquinin. Hydroxyethylhydrocuprein lags somewhat in its protective power, except in the large dose of 2 mg., where the difference is not great.

Summary. Our work, therefore, confirms what Miura and Okamoto stated in reference to the superior protective power of ethylapoquinin over optochin in experimental pneumococcus infection of mice. We have noted that ethylapoquinin varies considerably in its toxicity depending upon its chemical purity. The lessened toxicity fortunately does not diminish its protective power. Clearly these variations in the different samples of ethylapoquinin must be taken into consideration in interpreting the results of experimentation, and most decidedly this must be remembered if later this derivative is to be used clinically. It is noteworthy that the estimation of the degree of levorotatory power in ethylapoquinin has been of value as a physical test for the toxicity of the derivative. The chemists believe that this physical property will be of great aid in the actual preparation of this substance, which can be very toxic in its action on animals if impure.

Of the two new derivatives, hydroxyethylapoquinin is the more important. This preparation has less toxicity than any of the ethylapoquinins and greater antipneumococcic power than any of them except 15. According to our data the latter preparation (15) was as toxic as optochin. The low toxicity of hydroxyethylapoquinin combined with its high protective power as indicated by the experimental results show it to be superior to the ethylapoquinins. Hydroxyethylhydrocuprein is the least toxic and although its protective action is not as great as any of the other derivatives described above, yet its low toxicity makes this compound of definite interest.

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THE DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE OF THE CREATIN-CREATININ METABOLISM IN VARIOUS MYOPATHIES BEFORE AND AFTER AMINO-ACID THERAPY.*

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Since the introduction of amino-acid therapy in the treatment of muscular dystrophies and atrophies, conflicting reports have appeared in the literature. A review of our treated cases and those of other workers[1] shows that studies on creatin-creatinin metabolism have been made which we believe important. It may be somewhat difficult for the clinician to distinguish between the myopathies due to abiotrophic changes in the muscles themselves and those due to nerve injury. Also there are no definite criteria by which to predict the results in any given case before amino-acid therapy is begun or after its administration over a short period of time. There are several factors which may influence the prognosis in a given case. These are the type and duration of the disease, the age of the patient, coëxisting infections and other systemic diseases and the amount of functional muscle tissue remaining in the patient. Our review of the results achieved leads us to believe that, after consideration of these factors, a study of creatinuria may prove a real aid in the early diagnosis and prediction of the therapeutic result possible in a particular case.

Direct chemical and histologic studies of the diseased muscles before and after amino-acid therapy may also yield information of much prognostic value. Such studies have been made by Tripoli and Beard,[1] Milhorat[2] and by Reinhold and coworkers.[3] The latter investigators showed that, in cases of advanced muscular dystrophy, a reduction in the concentration of various muscular constituents to about 5 or 10% of their normal value occurred, while in earlier cases this reduction amounted to but 50% of the normal value. Most conspicuous was the reduction in the creatin content of the muscle. After glycin therapy a restoration of the muscle constitu-

* A preliminary report of these studies was presented before the Biochemical Division of the American Chemical Society at the 87th meeting, St. Petersburg, Fla., March 27, 1934.

ents took place, especially of total nitrogen and of creatin. Histologic studies were in accord with these chemical findings.

We wish to present in this paper our observations on creatin-creatinin metabolism in 30 of our cases,[1,4] with especial reference to the relationship between the creatinuria and the diagnosis and prognosis following the institution of amino-acid therapy.

Methods. The daily excretion of total creatinin, preformed creatinin and creatin in the urine was studied during a control period of 5 days. At the end of this time from 10 to 15 gm. of glycin or glutamic acid were given daily in water, milk or fruit juice. No change was made in the usual diet of the patients. The effect of this treatment upon the excretion of the creatin bodies was studied in 24-hour specimens of urine for 3 similar periods of 5 days each. Total creatinin was determined by the method of Benedict and Myers[5] and preformed creatinin by the method of Folin.[6] The daily excretion of total creatinin minus the excretion of the preformed creatinin times 1.16 is equivalent to the daily creatin output.

TABLE 1.—CREATIN-CREATININ METABOLISM IN VARIOUS MYOPATHIES AFTER AMINO-ACID THERAPY. (AVERAGE 24-HOUR EXCRETION IN DIFFERENT PERIODS.) (AVERAGE VALUES FOR EACH GROUP.) (BEARD, ANDES AND TRIPOLI.)

Patient No.	Age, years.	Control period.			Amino acid, 10–15 gm. daily.	First period.			Second period.			Third period.		
		Total creatinin	Preformed creatinin.	Creatin.		Total creatinin.	Preformed creatinin.	Creatin.	Total creatinin.	Preformed creatinin.	Creatin.	Total creatinin.	Preformed creatinin.	Creatin.
		gm.	gm.	gm.		gm.	gm.	gm.	gm.	gm.	gm.	gm.	gm.	gm.
Group 1 1–10*	8–37	1.17	0.73	0.50	Glutamic acid or glycin	1.38	0.72	0.77	1.16	0.56	0.10	1.14	0.65	0.57
					% Increase	18.0	None	54.0	None	None	40.0	None	None	16.0
Group 2 11–17†	12–54	1.15	0.82	0.38	Glutamic acid or glycin	1.72	1.08	0.74	1.38	0.99	0.45	0.97	0.81	0.18
					% Increase	49.5	32.9	94.7	20.0	20.7	15.8	None	None	None
Group 3 18–30‡	7–55	1.49	0.94	0.64	Glutamic acid or glycin	1.64	1.07	0.66	1.53	1.08	0.52	1.32	0.92	0.46
					% Increase	10.0	13.8	None	2.7	14.9	None	None	None	None

RESULTS.—Group 1, objective and subjective improvement; Group 2, subjective improvement; Group 3, no improvement.

* Cases 1 to 10 were: Pseudohypertrophic muscular dystrophy, 4; progressive muscular dystrophy, 3; and 1 each of "Psychopathic inferiority complex" (disuse atrophy), early spinomuscular atrophy and strabismus.

† Cases 11 to 17 were: Amyotrophic lateral sclerosis, 4; and 1 each of hypothyroid-hypopituitary, multiple sclerosis and spinomuscular dystrophy.

‡ Cases 18 to 30 were: Pseudohypertrophic muscular dystrophy, 3; progressive spinomuscular atrophy, 2; poliomyelitis, 2; and 1 each of "Friedreich's ataxia," tabes dorsalis with muscular dystrophy, muscular atrophy following radial nerve injury, von Recklinghausen's disease, "Jamaica ginger paralysis" and paresis with muscular atrophy.

Results and Discussion. The average results obtained are listed in Table 1. For purposes of comparison we may divide the cases into 3 groups, as follows:

GROUP 1 (Cases 1 to 10). Patients in whom the average creatin excretion rose from 50 to 200% above that of the control period

(provided this increased creatinuria soon disappeared in the third or subsequent period), showed both subjective and objective improvement. Cases 8 and 10 were the exceptions. In the latter the amino-acid therapy apparently helped the patient to retain the large amount of creatin excreted daily.

GROUP 2 (Cases 11 to 17). Some neuromuscular patients, who showed about the same degree of increase and decrease in creatinuria as those of Group 1, showed only subjective improvement or had arrest of progress of their clinical symptoms.

GROUP 3 (Cases 18 to 30). Patients in which no increased creatinuria occurred, or where it was less than 50% above that observed in the control period, showed no improvement. Exceptions were Cases 18 and 25.

The correlation of the increased creatinuria with clinical improvement is further shown in the observations of other investigators[2,9,10,11,12] in this field (Table 2).

TABLE 2.—THE PROGNOSTIC SIGNIFICANCE OF CREATINURIA IN CASES OF VARIOUS MYOPATHIES DURING AMINO-ACID THERAPY. (COMBINED RESULTS OF OTHER AUTHORS.)

Myopathy.	No. of cases.	Creatinurea.	Clinical results.	Observer.
Progressive muscular dystrophy	3	++	Marked improvement	Milhorat, Techner and Thomas.[10]
Progressive muscular dystrophy	14	++	Marked improvement	Milhorat.[2]
Progressive muscular dystrophy	7	++	Good improvement	Kostakow and Slauck.[11]
Pseudohypertrophic muscular atrophy	3	++	Marked improvement	Milhorat, Techner and Thomas.[10]
Myasthenia gravis	20	+++	Marked improvement	Boothby.[9]
Pseudohypertrophic muscular dystrophy	2	++	Good improvement	Mettel and Slocum.[12]

Creatin Excretion. The average variation of the creatinuria before amino-acid therapy was from 0.07 to 1.63 gm. in the 17 cases which improved or in which the progress of the disease had been arrested. In the remaining 13 cases which showed no improvement the average creatin excretion varied from 0.0 to 1.43 gm. Thus the degree of initial creatinuria seems to bear little relation to the subsequent clinical improvement in the patient after amino-acid therapy.

Most of our patients who improved showed an excellent ability to form creatin from the amino acids. This confirms the fact that the metabolic fault of the myopathy patient is not the inability to form creatin, but an inability to retain and utilize the creatin in the muscles. A subsequent disappearance of the creatinuria and

storage of creatin in the muscles is then associated with clinical improvement.

It is significant from the diagnostic and prognostic points of view that no increased creatinuria (above 50% of that of the control period) after amino-acid therapy was observed in Cases 18 to 30, most of which were suffering from neuromuscular conditions. This evidently indicates that the lower motor neurone (trophic unit) with the muscle it innervates is necessary, not only for the functional activity of the muscle, but also for creatin formation from amino acids. We believe that this lack of increased creatinuria after amino-acid therapy may prove to be a real aid in distinguishing the neuromuscular conditions from the muscular dystrophies. Possibly this fact may also explain why very little, if any, objective improvement is to be expected in these neuromuscular conditions, whereas in the muscular dystrophies and particularly in cases of myasthenia gravis which are probably primarily muscular conditions, objective improvement may and does occur after amino-acid therapy. If the above reasoning is correct, it would seem that, from the metabolic point of view, the 4 cases of amyotrophic lateral sclerosis (Cases 11 to 14) would stand midway between the dystrophies and the other neuromuscular conditions, even though they are muscular diseases due to lesions in the central nervous system. In these cases increased creatin formation and excretion were associated with only subjective improvement.

Harris and Brand[7] stated that their patients with muscular dystrophy usually excreted larger amounts of creatin than comparable patients suffering from neuromuscular conditions. The average creatin excretion of our first 10 cases suffering from dystrophies was 0.50 gm.; in the 15 neuromuscular cases it was 0.73 gm. Thus the initial creatinuria in both types of diseases was about the same.

Adams,[8] in a preliminary paper, stated that the increase in creatin after glycin therapy appears to be proportional to the degree of creatinuria before glycin is administered. The creatin excretion, before amino-acid therapy in the 30 cases reported in this paper, was practically constant from day to day in 20 patients, while in the remaining 10 it varied from 50 to 200%. The data for our 16 cases which showed subjective and objective improvement show that the ability of the patient to form, utilize, or excrete creatin is probably not necessarily dependent upon the degree of his creatinuria before amino-acid therapy is begun, but rather upon the degree of increased and decreased creatinuria after the therapy is instituted.

Creatinin Excretion. The average variation in the daily preformed creatinin excretion before amino-acid therapy was from 0.15 gm. to 1.69 gm. Accepting 1.50 gm. as about the normal daily creatinin excretion we had 5 patients who excreted from 1.50 to 1.70 gm.; 6 from 1 to 1.50 gm. and 19 below 1 gm. The

average daily amount excreted by all patients was 0.85 gm. This confirms the well-known fact that the creatinin excretion is below normal in different types of myopathies. In 18 patients the daily creatinin excretion was practically constant, while in 12 patients it varied from 0.15 to 1.30 gm.

It is generally believed that the creatinin output is not affected in the myopathies after amino-acid therapy. Our previous results and those of several others[13,14] show definitely that the creatinin output can be increased in normal animals and man, as well as in the myopathies after amino-acid therapy. In 15 patients reported in this paper the creatinin excretion increased from 11 to 67% above that of the control period after amino-acid therapy. This affords additional evidence of the exogenous origin of creatinin from the amino acids of the diet.

TABLE 3.—THE EFFECT OF AMINO-ACID INGESTION UPON THE DISTRIBUTION OF NITROGEN IN THE URINE IN DIFFERENT MYOPATHIES. AVERAGE VALUES.

	Substance.	Control period.			First period.			Second period.			Third period.		
		Amount, gm.	Nitrogen content.	Per cent of total N.	Amount, gm.	Nitrogen content.	Per cent of total N.	Amount, gm.	Nitrogen content.	Per cent of total N.	Amount, gm.	Nitrogen content.	Per cent of total N.
B	Total N	....	14.40	...	....	17.55	...	....	15.13	...	....	14.03	
Amyotrophic	Urea	25.59	11.93	82.4	31.61	14.74	84.0	27.46	12.81	84.7	24.97	11.65	82.9
lateral	Ammonia	0.90	0.74	5.1	1.01	0.84	4.8	0.80	0.66	4.4	0.77	0.64	4.6
sclerosis	Uric acid	0.55	0.18	1.3	0.61	0.20	1.2	0.47	0.16	1.0	0.41	0.14	1.0
	Creatinin	1.55	0.57	4.0	2.08	0.77	4.5	1.87	0.69	4.6	1.78	0.66	4.7
	Creatin	0.56	0.18	1.3	0.94	0.31	1.7	0.17	0.06	0.3	0.18	0.20	1.4
	Undetermined N by difference	....	0.79	5.8	....	0.70	4.0	....	0.75	4.9	....	0.75	5.4
G	Total N	....	10.71	...	....	11.08	...	....	10.62	...	....	9.98	
Tabes	Urea	18.22	8.51	79.4	18.98	8.85	79.6	18.65	8.70	81.9	17.33	8.08	81.0
dorsalis	Ammonia	0.68	0.58	5.2	0.48	0.37	5.4	0.60	0.49	4.6	0.50	0.41	4.1
	Uric acid	0.47	0.15	1.8	0.49	0.16	1.4	0.39	0.13	1.2	0.33	0.11	0.9
	Creatinin	1.42	0.56	5.3	1.56	0.60	5.3	1.47	0.54	5.1	1.30	0.49	4.9
	Creatin	0.98	0.31	2.4	0.30	0.10	0.8	0.73	0.24	2.3	0.11	0.03	0.3
	Undetermined N by difference	....	0.63	5.7	....	0.79	7.2	....	0.52	4.8	....	0.86	8.6
G	Total N	....	7.73	...	....	8.53	...	....	8.55	...	....	8.30	
Progressive	Urea	12.49	5.83	74.9	14.05	6.55	76.6	14.40	6.73	78.5	14.50	6.76	81.2
muscular	Ammonia	0.68	0.57	7.4	0.90	0.74	8.9	0.79	0.65	7.6	0.67	0.55	6.8
dystrophy	Uric acid	0.34	0.12	1.5	0.36	0.12	0.1	0.37	0.18	1.4	0.33	0.11	1.3
	Creatinin	0.58	0.22	2.8	0.46	0.17	2.1	0.45	0.20	2.0	0.45	0.17	2.2
	Creatin	1.09	0.34	4.3	0.68	0.21	2.5	0.76	0.25	2.8	0.65	0.21	2.4
	Undetermined N by difference	....	0.67	8.9	....	0.72	8.4	....	0.54	7.4	....	0.48	6.9

In 3 of our cases we made a study of the effect of amino-acid ingestion upon the distribution of nitrogen in the urine in the form of total, urea, ammonia, uric acid, creatin, creatinin and undetermined nitrogen (Table 3). There was no significant change during the first period after amino-acid ingestion in the excretion of the total, urea, ammonia and uric acid nitrogen in the 3 cases, with the possible exception of a slight rise in the first period in the total and urea nitrogen in the case of amyotrophic lateral sclerosis. In

this case there was also an increase of 45% in creatin excretion which later disappeared. The increase in creatinin excretion was 40, 26 and 17% greater in the 3 experimental periods than it was in the control period. In the case of tabes dorsalis there was a 32% increase in creatin excretion in the first experimental period with no corresponding increase in creatinin excretion. In case of progressive pseudohypertrophic muscular dystrophy there was no increased creatin or creatinin excretion. These results are in accord with the observations of Adams,[8] who observed that in a case of myasthenia gravis no significant changes occurred in nitrogen, phosphorus or sulphur balance after amino-acid ingestion.

It is significant here that in 1 case there was an increased creatinin output with no corresponding change in excretion of other nitrogenous substances, while in the other 2 cases, despite the increased amino-acid intake, no corresponding increase in different forms of nitrogen was noted. This observation in the latter 2 cases may be explained by a lack of amino-acid absorption or a defect in protein metabolism, as evidenced by the work of other investigators.[3] Further studies in this direction are contemplated.

Our studies confirm and extend those of Milhorat,[2] who observed increased creatinuria after glycin administration in cases of muscular dystrophy but not in cases of secondary muscular atrophy. Milhorat pointed out that glycin was helpful in the differential diagnosis between the primary myopathies and secondary degenerations.

Summary. The creatin and creatinin excretion in the urine of 30 of our 46 patients suffering from various myopathies has been studied before and after the institution of amino-acid therapy.

Both subjective and objective clinical improvement were observed in 10 patients and subjective improvement only in 7 patients whose creatin excretion rose from 50 to 200% above that of the control period, provided this increased creatinuria soon disappeared or returned to the control level. In 4 other cases, the progress of the disease was arrested.

No clinical improvement took place in 13 cases, 9 of which were suffering from neuromuscular conditions, in which increased creatinuria was absent or less than 50% above that of the control period.

The possible diagnostic and prognostic significance of these creatinuria studies in the myopathies treated with amino acids is discussed.

The results of these studies again confirm our view that both creatin and creatinin may have an exogenous origin from the amino acids of the diet.

Amino-acid therapy had little effect upon the distribution of nitrogen in the urine of 3 cases in the form of the total, urea, ammonia, uric acid and undetermined nitrogen. The increase in creatin and creatinin excretion was affected in only 1 of these cases.

Evidence is presented that the lower motor neurone (tropic unit) with the muscle it innervates must be functionally intact for creatin formation from the amino acids.

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ARTERIOLAR ESSENTIAL HYPERTENSION AND ACTIVE TUBERCULOSIS: THEIR RARE ASSOCIATION.

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It has often been noted that active tuberculosis and arteriolar essential hypertension are rarely found together.[1–5] Of the more recent and accurate studies of blood pressure in tuberculosis, Grant,[6] in 1921, found that 5 of 140 patients with pulmonary tuberculosis had a systolic blood pressure above 150 mm. Betchov and Farbarge-Vail[7] noted that only 1 of 157 tuberculous patients had a sytolic blood pressure above 150 mm. Stivelman[8] found that 10% of 464 tuberculous patients, from 16 to 30 years of age, had blood pressures over 135 mm. and over 140 mm. in older patients. He did not present the actual readings, and it is possible that most of these elevations were between 135 and 150 mm. Masten[4,9] strengthens this possibility by finding that of 230 tuberculous patients, 6.5% had blood pressures above the average normal; yet, only 2.6% had systolic pressures 150 mm. or more. In 504 cases of active tuberculosis, Bunta[4,5] found only 1 case with "absolute hypertension;" 146 systolic, 88 diastolic. Of 240 cases of active tuberculosis seen by the author, not 1 patient with a blood pressure above 150 mm. was encountered.

The reasons for the rare association of the two diseases are not conclusive. Although essential hypertension is chiefly a disease of midlife, and active tuberculosis primarily a disease of the first three decades, there are many middle-aged persons with active tuberculosis. Of 212 tuberculous patients, the author found that 39% were over 40 and 13% were over 50 years of age; yet hypertension was not encountered. It is possible that the tuberculous toxemia has a hypotensive action and lowers a previously high blood pressure. It is also to be noted that the two diseases tend to occur in different physical types, the hypertensive patient tending to have a short thick neck and a short wide thorax, whereas active tuberculosis tends to occur in the long lean person. It is possible that the former type is more capable of resisting tuberculosis.[4] Finally, it is stated that on the uncommon occasions when arteriolar hypertension and active tuberculosis occur together, the tuberculosis is apt to be mild, of the fibroid type and but slightly progressive.[1,2,3,6,7]

It is clear that the two diseases occur together rarely, and when they do, the tuberculosis tends to be mild. It is important to know (1) whether hypertensive patients really have had tuberculous infection in early life as often as non-hypertensive people, and (2) what is the nature of the apparently greater resistance of the hypertensive patient to active tuberculosis.

Present Study. Since it is known that from 80% to 100% of adults have positive skin reactions to tuberculin[10] and have postmortem findings of healed tuberculosis,[11] it would seem likely that most if not all hypertensive patients would also have such evidence of old tuberculous infection. Yet it is possible that a much lower incidence of positive tuberculin reactions and of healed tuberculosis at postmortem might be found in hypertensive patients. This possibility has been checked by (1) analyzing for tuberculosis the family history, past history and postmortem findings in a group of hypertensive patients, and (2) carrying out the routine intracutaneous tuberculin test in a group of hypertensive patients.

To determine whether the hypertensive patient has a different degree of resistance or immunity to tuberculosis, the tuberculin test has been utilized further. The relationship of the intracutaneous tuberculin reaction to immunity and resistance is not settled. Many believe that the tuberculin reaction and immunity tend to parallel each other.[12] Yet it has recently been reported that a high degree of reaction to tuberculoprotein seems to hasten the progress of tuberculosis rather than increase resistance.[13] Whichever of these conflicting ideas is correct, it would be of value to know whether hypertensive patients react to tuberculin in a greater or lesser degree than non-hypertensive persons. Therefore, in the present study, instead of using only the usual 1 to 1000 dilution

of tuberculin, dilutions up to 1 to 100,000 were used in order to note any difference in reaction between hypertensive and non-hypertensive persons.

The patients used in this study were: (1) Hypertensive ward patients with blood pressure readings of 160 systolic, 90 diastolic or more; and (2) ward patients beyond the age of 45, in whom the blood pressure was systolic 130 or less and diastolic less than 90 mm.

Results. 1. *Family and Past Histories of Tuberculosis in Hypertensive Patients.* Analysis of the records of 190 ward patients with essential hypertension and of 101 ward patients with normal blood pressure, and beyond the age of 45, showed a similar incidence of pleurisy, past and family histories for tuberculosis (Table 1).

TABLE 1.—INCIDENCE OF TUBERCULOUS HISTORIES IN (1) HYPERTENSIVE PERSONS, AND (2) PERSONS WITH NORMAL BLOOD PRESSURE.

	Family history of tuberculosis. %	Past history of tuberculosis. %	Past history of pleurisy. %
190 hypertensives	16	1.6	3.2
101 controls	21	3.0	0

2. *Postmortem Evidence of Tuberculosis in Essential Hypertension.* The postmortem records of 80 patients with essential hypertension were analyzed for evidence of tuberculosis. Of the 80 patients, 56 died of heart failure or cerebral hemorrhage; 10 of the 80 died of lobar or bronchopneumonia; the remaining 14 of cancer, cirrhosis of liver, etc. In 46 of the 80 cases, the pleura had old fibrous adhesions over the upper lobe, usually at the apices, and often in both lungs. Cases with fresh adhesions or adhesions at the bases only were not included in the above 46 cases. In 14 of the 80 cases there was a family history of tuberculosis, and in 10 of the 14, adhesions were present but in no more abundance than in those with no family history of tuberculosis. In 19 of the 80 cases there were grossly calcified areas seen in the lung parenchyma. In 6 other cases, microscopic evidence of tuberculosis of the hilar or mesenteric glands was found. In 1 of these cases, caseous necrosis was seen, while from another case an injection of gland material into a guinea pig gave positive results for active tuberculosis. In the latter case there was no clinical evidence of active tuberculosis.

3. *Reactions of Hypertensive Patients to Different Dilutions of Old Tuberculin.* A group of 40 ward hypertensive patients, average age of 58, and 55 ward patients with normal blood pressure, average age of 50, were studied with varying dilutions of intracutaneous tuberculin injections. The dilutions and amount used were 0.1 cc. of 1 to 1000, 1 to 10,000, 1 to 50,000 and 1 to 100,000. Each patient received the 4 injections at one time at separate sites on the forearms. At the end of 48 hours the reactions were read in

millimeters in three dimensions. Any area of induration was considered a positive reaction.

As seen in Table 2, there was a similar percentage both of positive reactions and of size of reactions to the varying dilutions, in the hypertensive persons as compared with the patients with normal blood pressure. In general, there was no significant difference in the amount of elevation of induration in either group of patients.

TABLE 2.—POSITIVE REACTIONS TO TUBERCULIN IN HYPERTENSIVE PERSONS AND THOSE WITH NORMAL BLOOD PRESSURE.

Dilution of tuberculin	1 to 1000	1 to 10,000	1 to 50,000	1 to 100,000
Positive reactions, %:				
40 hypertensives	90.0	55.0	42.0	30.0
55 controls	91.0	61.0	33.0	26.0
Average diameter of reactions, mm.:				
40 hypertensives	19.0	10.9	5.7	6.0
55 controls	16.6	8.0	5.2	5.7

Summary and Conclusions. Analyses of postmortem findings, and of the past and family histories showed that the hypertensive patients had tuberculous infection at some time in life. Studies with tuberculin showed that 90% of the hypertensive patients and 91 per cent of the controls with normal blood pressure had tuberculous infection at some time in the past. The analyses of the reactions to the 1 to 10,000, 1 to 50,000 and 1 to 100,000 dilutions of tuberculin, used in an effort to disclose different degrees of sensitiveness or resistance, showed no significant difference in frequency or size of reaction in the hypertensive patients as compared with the control subjects. Therefore, while clinical experience indicates that arteriolar essential hypertension and active tuberculosis occur together uncommonly, the present study does not supply the reason for this observation.

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DELAYED RESOLUTION IN LOBAR PNEUMONIA AND ITS RELATIONSHIP TO PREËXISTING SYPHILIS.

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The conception that syphilis predisposes to the complications of acute lobar pneumonia and particularly to delayed resolution has been advanced by Fitz-Hugh,[1] Kampmeier[2], and Youmans and Kampmeier.[3] Others, for example Lieven,[4] are not in accord with this view. In the reports of each of the above-mentioned authors the number of patients studied is relatively small. It seemed desirable to evaluate the possibility that syphilis may be a factor in predisposing to delay of resolution in lobar pneumonia, and an analysis of 509 cases is reported in this communication. The recent occurrence on the wards of the Johns Hopkins Hospital within a period of 2 months of 3 cases of unresolved pneumonia in patients with syphilis gave an added impetus to this study.

Material. The material for this analysis includes: (1) All cases of acute lobar pneumonia admitted to the Johns Hopkins Hospital for the 8-year period ending, May, 1933; (2) all the cases of acute lobar pneumonia admitted to the Vanderbilt University Hospital for the same period; (3) all patients with this infection admitted to the Baltimore City Hospital for the years 1929–1932, inclusive; (4) certain observations also were made on all the cases in the files of the Pathological Department of the Johns Hopkins Hospital with a necropsy diagnosis of chronic fibroid pneumonia, bronchiectasis, lung abscess, organizing pneumonia or unresolved pneumonia for the 7-year period ending, May, 1931.

We selected 509 cases of acute lobar pneumonia from almost 900 protocols, including only those records in which the Wassermann reaction on the blood serum had been recorded, in which there was no antecedent pulmonary disease, such as tuberculosis, and in which there was no question whatever of the diagnosis of lobar pneumonia. The clinical symptoms and signs were essentially characteristic in each instance. Demonstration of the etiologic pneumococcus was obtained in the majority of the cases. Patients treated with Type I antipneumococcus serum are excluded.

Analysis of Cases of Lobar Pneumonia. The patients are almost equally distributed in number between the white and colored races—white, 262 (51.5%); colored, 247 (48.5%). Of the entire group, 139 (27.3%) had syphilis; 50.2% of the colored group were syphilitic as compared with 6.9% of the white patients. The 4 main groups

of pneumococcus appear with equal frequency in the syphilitic and non-syphilitic cases.

The cases are arbitrarily placed for study into 4 main clinical groups according to the clinical outcome: (1) Crisis; (2) lysis in 7 days or less; (3) lysis in 7 to 14 days; (4) lysis in 15 or more days.

Crisis. In this group are placed those patients in whom the acute phase of the disease terminated by fairly abrupt clinical improvement characterized by a sharp fall in the temperature, pulse and respiratory rate, and followed shortly by a disappearance of abnormal physical signs. Termination of the pneumonia by crisis occurred in 141 (27.7%) of the 509 patients. This phenomenon occurred in 39 (28%) of the group with syphilis and in 103 (27.5%) of the non-syphilitics. In patients with syphilis, crisis occurred in an average of 7.2 days, and in the non-syphilitic group, in 7 days.

TABLE 1.—CLINICAL OUTCOME OF PNEUMONIA IN SYPHILITIC AND NON-SYPHILITIC CASES.

	Clinical outcome.	
	Total syphilitic, 139 cases.	Total non-syphilitic, 370 cases.
Crisis	39 (28.0%)	102 (27.5%)
Lysis in less than 7 days	26 (17.0%)	88 (23.7%)
Lysis in 7 to 14 days	9 (6.4%)	34 (9.1%)
Lysis in more than 15 days "unresolved pneumonia"	15 (10.7%)	30 (8.1%)
Empyema	5 (3.6%)	23 (6.2%)
Died:		
Pneumonia or direct complications	31 (22.3%)	74 (20.0%)
Pneumonia complicated by other diseases	14 (10.0%)	19 (5.1%)

Lysis in less than 7 days: In this group are included those patients in whom the pneumonia underwent a less abrupt clinical improvement. The physical signs cleared and the temperature and pulse fell gradually to normal over a period of 7 days or less. Such resolution occurred in 26 (17%) of the syphilitics and in 88 (23.7%) of those without syphilis.

Lysis in 7 to 14 days: This classification includes those patients in whom termination of the disease was associated with a gradual defervescence of fever and pulse rate and the clearing of abnormal clinical and roentgenologic signs over a period of 2 weeks from the beginning of recovery. This type of healing occurred in 9 (6.4%) of the group with syphilis and in 34 (9.1%) of those without this infection.

Lysis in 15 days or more: In this group are included those patients who, though much improved or essentially clinically well, continued to exhibit abnormal physical signs or substantial changes in the Roentgen ray films of the chest for more than 2 weeks after the termination of the acute phase of the illness. Such a classification is designed to include those cases ordinarily diagnosed as "delayed resolution" or "unresolved pneumonia." Of the 45

patients in this group, 15 had syphilis and 30 had not. Of the 139 cases in the entire series with syphilis, 10.7% showed such a retarded resolution as compared with 8.1% of the 370 patients who were non-syphilitic. The age distribution of the patients in this class paralleled roughly that of the whole group. No particular lobe of the lung seemed to be involved with undue frequency. The occurrence of the various types of pneumococci in these cases corresponded quite closely with their frequency in the entire series, except for the pneumococcus Group III which occurred but once.

Other Complications of Pneumonia. Bacteremia was noted with about equal frequency among the syphilitics and the non-syphilitics with pneumonia. Empyema occurred in 28 of the 509 cases. This complication was present in 23 (6.2%) of the non-syphilitic group in contrast to 5 instances of it (3.6%) in the group with syphilis. It is of interest that empyema occurred 3.5 times as frequently in the white race as in the colored (22 in 262 white patients; 6 in 247 colored patients). Of the 4 cases which developed lung abscesses, 2 were syphilitic and 2 non-syphilitic. Bronchiectasis was not noted as a sequel of pneumonia, though in many instances the patients were not followed for a period sufficiently long to note the development of such late complications.

Mortality. Of the 509 patients reviewed in this series, 138 (27.1%) died. Of these, 105 died directly of pneumonia or complications of this infection (pneumococcus endocarditis, pericarditis, empyema, etc.), while the other 33 patients exhibited associated illnesses which contributed to death (heart disease, diabetes mellitus, etc.). Of the 105 patients who died of pneumonia or its direct complications, there was proportionate distribution among the syphilitics—31 cases (22.3%)—and the non-syphilitics—74 (20%).

Necropsy Data. An attempt was made to determine whether any relationship existed between syphilis and chronic pulmonary infection other than that directly attributable to an antecedent attack of acute lobar pneumonia. For this purpose the autopsy records of the Johns Hopkins Hospital were reviewed for the 7-year period ending, May, 1931. The lesions included in this survey were those indexed as chronic fibroid pneumonia, lung abscess, empyema, bronchiectasis and organizing pneumonia. The following groups of cases were excluded: (1) Infants and children under 15 years of age and all those above this age with congenital syphilis, since this study is concerned only with acquired syphilis; (2) all patients in whom some obvious extrathoracic focus was the source of metastatic pulmonary infection; (3) tumors of the mediastinum producing bronchial obstruction with resultant bronchiectasis, a group which included several cases of aneurysm of the aorta; (4) pulmonary infection associated with neoplasm; (5) those cases in which the blood Wassermann reactions were not recorded in the clinical records; (6) all granulomatous infections of the lungs (tuberculosis,

fungus, infection, etc.); (7) all instances in which pulmonary infection was obviously fairly acute in its histologic appearance or less than 3 or 4 weeks' duration as judged from the clinical history. In short, the cases selected for study are those of chronic pulmonary infection of one form or another, other than those residual lesions directly traceable to lobar pneumonia.

During this 7-year period, 4000 necropsies were performed in the Johns Hopkins Hospital. After the groups indicated above are excluded, only 30 protocols of cases with chronic pulmonary infection remain for analysis. Of these, only 5 (16.6%) were syphilitic, a figure which is quite close to the general hospital incidence for this infection.[5] It appears from these data that there is no appreciable predisposing relationship between syphilis and chronic pulmonary infection as defined above.

Results of Antisyphilitic Treatment in Unresolved Pneumonia. Head and Seabloom,[6] in 1919, reported beneficial results following the administration of arsphenamin to 3 colored male syphilitic patients with unresolved pneumonia. The injections of the drug were started 4, 6 and 9 weeks, respectively, after the temperature became normal. These writers were of the opinion that the specific treatment hastened the process of resolution in these cases.

Four of the patients in this report, in whom resolution of pneumonia was delayed for over a month ("unresolved pneumonia"), received antisyphilitic treatment.

Case Abstracts. CASE 1.—A. T. (Unit No. 49201) contracted syphilis 2 years before the onset of pneumonia. He was given 8 injections of arsphenamin and 16 of a bismuth preparation over a period of 9 months, the last treatment being administered 9 weeks prior to the onset of his acute illness. He was admitted to the wards on the 4th day of pneumonia, with consolidation of all lobes of his lungs except the left upper. Group IV pneumococci were isolated from the sputum. The temperature began to drop on the 6th day of his illness, and, though it was quite normal 5 days later, resolution of the pulmonary consolidation was very much delayed. On the 31st day after the temperature had become normal he still showed extensive signs of unresolved pneumonia, though the process was slowly clearing. Potassium iodid, 6 gm. daily, was started at this time; and on the 40th afebrile day he received 0.3 gm. of neoarsphenamin intravenously. He then received arsphenamin, 0.4 gm., intravenously, once a week for 4 weeks. At the end of this time he still presented definite roentgenographic and physical signs of unresolved pneumonia at both bases. He was then given at weekly intervals 4 injections of bismuth salicylate, 0.2 gm., and then arsphenamin again for 3 weeks. At the end of this time a Roentgen ray film of the chest showed that the lungs were essentially clear but there was still demonstrable some percussion impairment and a few râles at both bases. Each of several observers felt that there was no conspicuous acceleration of absorption of the unresolved pneumonic process in this case after the institution of antisyphilitic treatment.

CASE 2.—R. A. (Unit No. 48665), a colored male, aged 45, was admitted on the 8th day of lobar pneumonia. He was very ill and showed physical signs indicating consolidation of his entire right lung. The temperature fell gradually to normal within a week and, although he felt quite well,

physical and roentgenographic signs had cleared but little. After the temperature had remained normal for 1 week he was given 3 gm. of potassium iodid a day and 0.2 gm. of bismuth salicylate intramuscularly every 5 days. This therapy was continued for 4 weeks, during which time slight resolution of the lung lesion was noted. He was then given 0.1 gm. neoarsphenamin intravenously (he had syphilitic aortitis and the initial treatment was accordingly mild), and was discharged to the Out-patient Department. He did not return, however, until 3 weeks later and at that time, though the Roentgen ray examination showed almost complete clearing, minimal signs of consolidation were still demonstrable.

A third patient is described here in considering the effect of antisyphilitic treatment, though he is not considered above in the analysis of clinical cases because he received antipneumococcus serum.

CASE 3.—J. P. (Unit No. 49363), a colored male, aged 24, developed a penile chancre for which he received 5 injections of arsphenamin. He failed to return to the clinic for further treatment for 2 months, after which time he returned with a neurorecurrence. He was then given 2 injections of 0.5 gm. arsphenamin at weekly intervals. Two days after the last injection he became acutely ill with lobar pneumonia. The illness was unusually severe. Group I pneumococci were cultured from his blood. He was treated with Felton's antipneumococcus serum. Abnormal physical signs and changes in the Roentgen ray persisted for some time after clinical improvement began and were still quite prominent 21 days after the beginning of resolution. He received 0.3 gm. of neoarsphenamin, and this dose was repeated 2 weeks later. Arsphenamin, 0.4 gm., was then given at weekly intervals. Throughout this period there was continued slow resolution of the lung lesion, and it was not until $1\frac{1}{2}$ months after the temperature became normal that the lungs were considered clear. None of several observers felt that treatment for syphilis had materially hastened the absorption of the pneumonic lesion.

CASE 4.—G. S. (Unit No. 41479), a colored female had been receiving antisyphilitic treatment steadily for 7 months prior to her admission to the hospital with pneumonia. She was admitted on the 3d and died on the 33d day of her illness. She was always acutely ill and the signs in the lungs changed but little during the period of observation. At necropsy she was found to have organizing pneumonia with extensive scarring of both lungs. She received no antisyphilitic treatment after she became acutely ill.

Discussion. Youmans and Kampmeier[3] reported that among 30 cases with postpneumonic complications, 12 (40%) were associated with preëxisting syphilis. In our series of 509 cases the clinical course of lobar pneumonia was not perceptibly different in patients with and without syphilis. A classical "crisis" occurred with the same frequency on the two groups. The incidence of delay of resolution beyond 15 days from the time of the beginning of recovery was not significantly greater in the syphilitic (10.7%) than the non-syphilitic (8.1%) patients. The mortality rates of those patients who died directly of the pneumococcus infection was essentially the same in those with and those without preëxisting syphilis. Of the patients in whom factors other than pneumonia contributed to death, it is quite to be expected that the death rate should be higher in those with syphilis for several patients who were

already quite ill with cardiovascular syphilis are here included. It was noted that empyema as a complication of lobar pneumonia is 3½ times as common among the whites as the colored. The total number is perhaps too small to warrant undue emphasis on this fact.

In 30 carefully selected necropsy-proved instances of chronic pulmonary infection, the incidence of evidence of syphilis is not appreciably higher than the frequency of this disease in the adult hospital population of the Johns Hopkins Hospital. It would appear that there is no undue association of chronic fibroid pneumonia, bronchiectasis, lung abscess or organizing pneumonia and the presence of antecedent infection with syphilis.

In 3 cases recorded there is little to indicate that treatment for syphilis accelerated appreciably the course of resolution of unresolved pneumonia. In a 4th case, resolution was delayed for a month until death in spite of vigorous and continuous treatment for syphilis, up to the time of the onset of pneumonia. It is true that in only 1 of the cases did the patient receive the large amounts of arsphenamin advised by Head and Seabloom,[6] but the administration of full therapeutic doses of this drug to patients with severe infections associated with anoxemia and the attendant liver damage seems to us not without risk. Though the so-called "nonspecific effect" of the arsphenamin, as a result of which non-syphilitic infectious processes undergo healing, was not noted in our cases, it is conceivable that large doses of the drug may facilitate the absorption of a chronic inflammatory process without any relation to its effect on syphilis.

Summary. 1. The records of 509 patients with acute lobar pneumonia are reviewed. Of these patients, 37.5% had syphilis. The clinical course of the pneumonia was not appreciably different in the syphilitic and non-syphilitic groups.

2. Following acute lobar pneumonia, delay of the process of resolution occurs about as frequently in the syphilitics as the non-syphilitics.

3. The records of 30 patients with necropsy diagnosis of chronic fibroid pneumonia, lung abscess empyema, bronchiectasis and organizing pneumonia, do not show any undue frequency of syphilis.

4. The reported favorable influence of antisyphilitic therapy on the course of unresolved pneumonia was not observed.

We express our thanks to Dr. Thomas R. Boggs for his kindness in placing the records of the Baltimore City Hospitals at our disposal, and to Dr. Joseph Earle Moore, Physician in Charge of the Syphilis Division, for his suggestions and advice.

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BOOK REVIEWS AND NOTICES.

DIE WERKE DES HIPPOKRATES. Herausgegeben von DR. MED. RICHARD KAPFERER unter Mitwirkung von PROF. DR. GEORG STICKER, Würzburg. Part 1. Sitten- und Standeslehre für Aerzte (Price, Rm. 2.80); Part 2. Die Altgewährte Kunst/Die Kunst (Price, Rm. 3); Part 5. Die Winde/Die Heilige Krankheit (Price, Rm. 1.50); Part 14. Die Hippokratischen Lehrsätze (Price, Rm. 2.10). Pp.: Parts 1 and 2, 59 each; Part 5, 65; Part 14, 80. Stuttgart: Hippokrates-Verlag G.M.B.H., 1934. (To be published in 25 parts costing ca. Rm. 100, card binding.)

HIPPOCRATES—or better the *Corpus Hippocraticum*—above all classical physicians has unquestionably held the highest position in the estimates of modern medical thought. This was not true, however, for the many centuries in which Galen, Celsus and Avicenna dominated medicine. With the advent of printing, for instance, Hippocrates' collected works were not printed until 1525; the others mentioned had numerous incunabula editions. By the 19th century, however, the position of the Father of Medicine was unassailably established. Between 1839 and 1861, Littré brought out his monumental "*Oeuvres*" in 20 volumes, which successfully utilized the available information to delineate a picture of Hippocratic medicine that still maintains. More useful to English readers is Jones' 4-volume edition in the Loeb Classical Library, with both Greek and English text, both of which we believe are accurate; yet for the scholar, adequate references to check this accuracy are lacking. Complete German editions have not hitherto been outstanding. Incomplete editions by Heiberg and by Ilberg and Kühlemann only partly remedied the situation, so that the announcement of this new German edition was received with lively anticipation. Sigerist has recently surveyed the situation in his customary illuminating manner (*Bull. Inst. Hist. Med.*, Johns Hopkins Univ., **2**, 190, 1934). Neohippocratism makes a new venture appropriately timely, yet one wishes that in the pamphlets thus far received there were more garnishings for the main dish. In these parts, preliminary remarks and footnotes are scantier than in Jones, and it becomes obvious that the work is more for the Neohippocratic reader than the scholar.

The present edition will present 75 books in 25 parts, the German text being based chiefly on the *Corpus Medicorum Grecorum*. The Greek text is not included. Of this collection, 4 parts have been received: 1. The Oath, the Law, Honorable Behavior, Precepts, the Physician; 2. Ancient Medicine and the Arts; 5. The Internal Airs or Breaths—The Sacred Disease (Epilepsy); 14. The Aphorisms. In the first of these are 5 propedeutic essays on the physician and his relation to the patient and to other doctors that will always have a practical as well as a historical value. The 2 essays of the second installment are noteworthy, one for the characteristic Hippocratic emphasis on observation rather than theory, the other because it is one recognized through the whole Christian era as most probably written by Hippocrates himself. The 2 works of Part 5 are The Internal Airs (or Breaths, in Jones' translation) and The Sacred Disease—Epilepsy. The Introduction explains that the former of these includes the concepts of inspired miasmatic air, intestinal gases and blood gases (oxygen, carbon dioxid), though the text hardly supports such a modern concept. This matter can be pursued in Axel Nelson's Upsala Dissertation (1909). The tract on Epilepsy is justly renowned, among other reasons, for its attribu-

tion of the disease to the central nervous system rather than to divine agencies. The ascription of the brain disorder and the convulsions to asphyxia also has an altogether modern ring.

The Aphorisms (Part 14), justly praised by the Editor for their divine-like quality, are preceded by an illuminating 12-page Introduction by Sticker. He points to the continued recognition of its great value from Erotian and Galen to Littré and Daremberg. Comprehension of Sticker's analysis of the Hippocratic theory of existence in health and disease, including such concepts as the life force (physis), its physiology and pathology, the physician's rôle in diagnosis, prognosis and therapy, will greatly aid in the understanding of any of the Hippocratic writings. We look forward with interest to the appearance of subsequent fasciculi.

E. K.

Clinical Aspects of the Electrocardiogram. By Harold E. B. Pardee, M.D., Assistant Professor of Clinical Medicine, Cornell University Medical College; Associate Attending Physician, New York Hospital; Consulting Cardiologist, Lying-in Hospital and Woman's Hospital, New York City. Pp. 295; 74 illustrations. Third edition, revised. New York: Paul B. Hoeber, Inc., 1933. Price, $5.50.

Although many have been asserting for some years now that the electrocardiogram has made most of its contributions to medicine, nevertheless the developments in the five years that have elapsed since the appearance of the second edition, have necessitated rewriting most of the chapters. The items chiefly requiring change were the *S-T* interval, the duration of the ventricular complex, large *Q* waves, the *T* wave and the changes resulting from myocardial disease. The author accepts the newer concepts of bundle-branch block and ventricular extrasystoles. The chapter on the theory of the electrocardiogram is especially to be recommended.

E. K.

Frontiers of Medicine (A Century of Progress Series). By Morris Fishbein, M.D. Pp. 207. Baltimore: The Williams & Wilkins Company, 1933. Price, $1.00.

This outline of medical progress since earliest times succeeds in presenting a readable story in its very narrow limits. In the earlier periods the author has wisely enlivened the narrative with quotations and has felt free to deal with topics according to his inclination or to his previous writings rather than based on the general importance of the subject. Thus the entertaining account of Paracelsus' life occupies 19 pages while Vesalius and Harvey are disposed of in a chapter of 4; Internal Medicine occupies 51 pages and Surgery 4; Pharmacology alone among the preclinical subjects has a chapter to itself. The Century of Progress, of which series the booklet is a unit, includes a good account of Beaumont and a paragraph on Chicago developments. The message of the Century of Progress Exposition is conveyed on the back of the jacket. The few hours required for reading this sketch will be well repaid.

E. K.

Lettsom. His Life, Times, Friends and Descendants. By James Johnston Abraham. Pp. 498; illustrated. London: William Heinemann, Ltd., 1933. Price, 30/ net.

One does not have to read the author's preface to realize that this biography of the great Quaker physician is a labor of love; the fact is evident in every page of this sumptuous volume. And a colorful life it

was to be depicted. From Lettsom's birth in the dwindling Quaker colony at Tortola in the West Indies, through his schooling in England, apprenticeship to the apothecary-surgeon, Sutcliff, of Settle, Yorkshire, "walking the wards" at St. Thomas', six months with Cullen, and an M.D. degree at Leyden, to his highly successful and philanthropic career in London, all is spread out for us with sufficient attention to detail and background to get a vivid picture both of the man and his times. As founder of the General Dispensary, Lettsom started a new era in the treatment of London's poor. A lifelong supporter of the Royal Humane Society, his quite modern publicity sense appears in the procession that he arranged around the room after the annual dinner of those "who had been raised from the dead." Lettsom's activities in much needed prison reform would alone be sufficient to preserve his fame, while the foundation of the Royal Sea Bathing Hospital—his most important medical contribution—is regarded as "the father of all the open-air sanatoria throughout the world" (p. 276). Founder of the famous Medical Society of London, he is perhaps best known to physicians through the frequently reprinted engraving of Lettsom presenting the deeds of No. 3 Bolt Court to the Medical Society. Perhaps even better known is the verse which, according to our author, has kept Lettsom's memory green. In the original of its more than 20 variants it reads:

"You say I'm dead, I say you lie,
I physics, bleeds and sweats 'em
If after that my patients die,
Why verily—J. Lets 'em."

E. K.

Collens System of Diet Writing, Including Diet Calculator, Obesity Chart, 100 Menu Prescription Forms. By William S. Collens, B.S., M.D., Chief, Diabetic Clinic, Israel Zion Hospital; Assistant Physician, Greenpoint Hospital; Metabolist, Brooklyn Women's Hospital; Consulting Metabolist, Rockaway Beach Hospital. New York: Form Publishing Company, 1933. Price, $5.00.

A device for calculating and prescribing quantitated diets for patients with such conditions as diabetes, nephritis, or obesity, that possesses the advantage of being simple, sufficiently accurate, very flexible in its range, convenient for the physician, and easily intelligible for the patient: quite the most practical device of the kind known to the Reviewer.

R. K.

The 1933 Year Book of Radiology. Diagnosis. Edited by Charles A. Waters, M.D., Associate in Roentgenology, Johns Hopkins University; Assistant Visiting Roentgenologist, Johns Hopkins Hospital. Therapeutics. Edited by Ira I. Kaplan, B.Sc., M.D., Director, Division of Cancer, Department of Hospitals, City of New York; Clinical Professor of Surgery, New York University and Bellevue Medical College. Pp. 804; 780 illustrations. Chicago, Ill.: The Year Book Publishers, Inc., 1933.

The same general plan, so successfully employed in the first of the series of Year Books, has again been utilized in this present volume. The book presents a résumé of the radiologic literature for the past year and appears to be even more comprehensive than the preceding contribution. This work should have a universal appeal, not alone for the radiologist but for all practitioners of medicine. There is no specialist or general practitioner who will not find much to interest him in this volume. It should serve a very useful purpose in keeping all abreast of the rapid advances being made in radiology. K. K.

MEDICINE IN PERSIA. By CYRIL ELGOOD, M.D., M.R.C.P., Late Physician to the British Legation, Teheran, Persia. Vol. 14 of Clio Medica. Pp. 105; 11 illustrations. New York: Paul B. Hoeber, Inc., 1934. Price, $1.50.

CLIO MEDICA has done wisely in adding a volume on Persian medicine to its valuable list of historical compends. Not many are aware of the fact that a large part of Arabian medicine is in reality Persian. The Arabs in conquering Persia not only displaced Zoroastrianism by Islamism, but they also substituted their language and script for the ancient Aryo-Persian. The great Arabian medical writers of the Middle East, of which Bagdad was for a long time the cultural center, were, as a rule, native Persians, although of diverse religions—Mohammedan, Jewish, Nestorian Christians. All used the Arabian language in their writings, just as French, German, English and Italians wrote in Latin during the Middle Ages.

The author, as physician to the British Legation in Teheran, had excellent opportunities, of which he made wise use, of acquainting himself with the medical history of Persia. He gives a good account of the great medieval epoch that produced men of the stamp of Rhazes, Avicenna, Haly Abbas and others, men whose influence upon the medicine of Western Europe was much greater than earlier historians believed. Avicenna's *Canon* was a textbook in Europe until the close of the seventeenth century. However, after the Tartar conquests, under Jenghiz Khan and Tamerlane, Persian medicine went into an eclipse from which it is just beginning to emerge. At the present time the custom of young Persians to complete their medical education in Beirut or Paris, together with the Pasteur Institute, founded at Teheran in 1921, have made medicine in modern Persia largely French. Persian art which reached so high a degree of perfection in former centuries has left many unusual anatomic drawings, some of which are reproduced in Elgood's book. D. R.

GERMAN MEDICINE. By W. HABERLING, M.D., Professor of the History of Medicine, Academy of Düsseldorf. Translated by JULES FREUND, M.D., Ex-Associate in Bacteriology, University of Pennsylvania. Vol. 13 of Clio Medica. Pp. 160; 9 illustrations. New York: Paul B. Hoeber, Inc., 1934. Price, $1.50.

IT is surprising how much of the history of German medicine the author has crowded into this little book. Beginning with primitive times, he carries us rapidly down through the Middle Ages to the modern period. The Middle Ages were far more sterile in German lands than in the Latin countries. For example, the great thirteenth century, so fertile in all directions—in literature, in art, in architecture—in France, in Italy and in Spain, had no counterpart in Germany. The great anatomist Vesalius was not appreciated in Germany until sometime after his death. It is, however, to the credit of German medicine that the doctrines of Harvey were at once espoused with great enthusiasm. The first real awakening came with Paracelsus; but after him, for nearly 200 years, there is no great original figure until Albrecht von Haller, a man of encyclopedic mind.

What Germany lost by its early slowness, by the depressing effects of the Thirty Years War, has been amply made up in the last 100 years. The pupil became the master. But will it remain so? Or will the return of medieval psychology affect the progress of science and medicine unfavorably? D. R.

INDUSTRIAL TOXICOLOGY. By ALICE HAMILTON, M.D. Pp. 329. New York: Harper & Brothers, 1934. Price, $3.

THE ever-increasing complexity and multiplicity of chemical processes in industry bring with them industrial hazards and poisonings which are bound to come under the observation of numerous practitioners of medicine. This handy pocket-size volume, written by the leading authority on the subject in this country, should be read by all physicians who practise in an industrial community. R. K.

DISEASES PECULIAR TO CIVILIZED MAN. By GEORGE CRILE, M.D. Edited by AMY ROWLAND. Pp. 427; 41 illustrations. New York: The Macmillan Company, 1934. Price, $5.

THE principle of orthogenesis ("straight creation") is explained as the mechanism whereby a species, beginning to vary definitely in a given direction, continues in that direction even if it thereby tends to its own destruction. It is here evoked "to account for the rise of the brain and the nervous system and the thyroid gland." Later the author adds the adrenals (why not also the pituitary, pancreas and gonads?) to his kinetic system, which in man's phylogenic development have become overactive, producing hyperthyroidism, neurocirculatory asthenia, peptic ulcer, diabetes (sometimes qualified as "probably")—"diseases peculiar to civilized man." Epilepsy, psychoneurosis and hypertension are also considered. The author recommends that this "hyperkineticism" be lessened by sympathectomy, thyroidectomy, adrenal denervation or rationalization. (N. B.—This term has not been defined here but is obviously not used in the customary sense of substituting plausibly rational motives for the protective reactions of the psychoneurotic.) His success with adrenal denervation in some 230 cases leads him to believe that the individual may be saved even though the species may be going on to destruction "by the same tool that enabled him to reach the greatest height of his civilization." More than half of the book is taken up with case histories, which also supply most of the evidence—of the sort that case histories are apt to supply. A proof of the truth of the principle of orthogenesis is fortunately not attempted. E. K.

WHO SHALL SURVIVE? A New Approach to the Problem of Human Interrelations. By J. L. MORENO, M.D. Pp. 437; illustrated. Washington, D. C.: Nervous and Mental Disease Publishing Company, 1934. Price, $4.

STUDIES were made from a public school, a state training school for girls and a neighborhood house in New York City. Whereas the psychoanalytic method is subjective, extending backward to past psychic trauma, this approach is through developing the individual's spontaneability with analysis of present performances together with appropriate environmental consideration.

It was observed that when children were free from supervision they arranged themselves roughly into three groups—isolates, pairs and those that adhered to leaders. Further studies were made by interviewing mothers, teachers and housemothers of cottages. The most informative data were obtained through "sociometric tests," wherein individuals choose the 5 girls they liked best, whether from their own cottage or from any other, and with these they then lived. The emotional reactions recorded through descriptions and graphs show attractions, mutual attractions, repulsions, mutual repulsions, indifferences, mutual indifferences and other interesting features.

The hypothesis, "that members of the superior class produce with members of the inferior class better offspring in general than when they remain in their own sphere," offers a ray of hope and it is intimated that, through planning, some of the unfit may propagate and thus modify or discard such palliative measures as sterilization.

Such constructive efforts may enable us to outsmart Nature!

N. Y.

PRACTICAL METHODS IN BIOCHEMISTRY. By FREDERICK C. KOCH, Professor of Physiological Chemistry, University of Chicago. Pp. 282; 17 illustrations. Baltimore: William Wood & Co., 1934. Price, $2.25.

THE author has drawn upon a large experience in preparing this manual of biochemical methods. Good features of the book include excellent fine-print discussions, a choice of several methods in many instances, and illustrations of the more complicated apparatus.

In the opinion of the Reviewer this manual should prove more suitable for a hospital laboratory than for a teaching course. Some of the methods presented are too long and complicated for general class use. The black type headings are often too informative. The data involved in the preparation of reagents used in the various methods are gathered in an appendix. This type of presentation would have advantages where technicians are employed, but appears inconvenient from the standpoint of proper teaching.

D. D.

THE LABORATORY NOTEBOOK METHOD IN TEACHING PHYSICAL DIAGNOSIS AND CLINICAL HISTORY RECORDING. By LOGAN CLENDENING, M.D., Professor of Clinical Medicine in the University of Kansas. Pp. 71. St. Louis: The C. V. Mosby Company, 1934. Price, 50 cents.

OBVIOUSLY the purpose of this laboratory notebook is to have each student record with care and without omissions his physical findings. While the Reviewer feels that the method of teaching recommended by the author is sound and appropriate, this notebook has no particular advantage over mimeographed sheets containing essentially similar headings. By the use of these headings the student can record his findings on blank paper unhandicapped by the abomination of printed forms and at the same time he is being trained to record his findings in a style which will later be acceptable as permanent hospital record.

S. L.

NEW BOOKS.

A Textbook of Histology. Functional Significance of Cells and Intercellular Substances. By E. V. COWDRY, Professor of Cytology, in the School of Medicine, Washington University, St. Louis. Pp. 503; 242 illustrations. Philadelphia: Lea & Febiger, 1934. Price, $5.50.

Jöns Jacob Berzelius. Autobiographical Notes Published by The Royal Swedish Academy of Sciences through H. G. SÖDERBAUM. Translated from the Swedish by OLOF LARSELL, Professor of Anatomy, University of Oregon Medical School, Portland. Pp. 194; illustrated. Baltimore: The Williams & Wilkins Company, 1934. Price, $2.50.

Clinical Toxicology. Modern Methods in the Diagnosis and Treatment of Poisoning. By ERICH LESCHKE, Professor of Internal Medicine in the University of Berlin. Translated by C. P. STEWART, M.Sc., PH.D., Lecturer in General Biochemistry, University of Edinburgh; Senior Biochemist, Edinburgh Royal Infirmary, and O. DORRER, PH.D., Research Assistant to Professor Wieland, Munich. Pp. 346; 25 illustrations. Baltimore: William Wood & Co., 1934. Price, $5.00.

Annals of the Pickett-Thomson Research Laboratory, Vol. 10, Monograph 16, Part 2, Influenza. With Special Reference to the Complications and Sequelæ, Bacteriology of Influenzal Pneumonia, Pathology, Epidemiological Data, Prevention and Treatment. By DAVID THOMSON, O.B.E., M.B., CH.B. (EDIN.), D.P.H. (CAMB.), Honorary Director, Pickett-Thomson Research Laboratory, St. Paul's Hospital, London, and ROBERT THOMSON, M.B., CH.B. (EDIN.), Pathologist to the Pickett-Thomson Research Laboratory. Pp. 916; illustrated. Baltimore: The Williams & Wilkins Company, 1934. Price, $17.50.

Bacteriologia. By DR. JOSÉ DE CARVALHO LIMA, Director of Institute of Bacteriology of São Paulo. Pp. 553; many colored illustrations. São Paulo, Impressora Paulista, 1933. (Price not given.)

Human Sterility. Causation, Diagnosis and Treatment. By SAMUEL RAYNOR MEAKER, M.D., Professor of Gynecology, Boston University School of Medicine; Gynecologist, Massachusetts Memorial Hospitals, etc. Pp. 276; 27 illustrations. Baltimore: The Williams & Wilkins Company, 1934. Price, $4.00.

Marriage Hygiene, Vol. 1, No. 1, August, 1934. First Issue. A Quarterly. Edited by A. P. PILLAY. Pp. 111; 3 illustrations. Bombay: The Times of India Press, 1934. Price, per issue, s. 4/6 or Rs. 2/8; Yearly, s 18/– or Rs. 10/–.

Hygiene for Freshmen. By ALFRED WORCESTER, A.M., M.D., Sc.D., Henry K. Oliver Professor of Hygiene, Harvard University. Pp. 151. Springfield, Ill.: Charles C Thomas, 1934. Price, $1.50.

NEW EDITIONS.

A Textbook of Pathology. By WILLIAM BOYD, M.D., M.R.C.P. (EDIN.), F.R.C.P. (LOND.), DIPL. PSYCH., F.R.C.S., Professor of Pathology in the University of Manitoba; Pathologist to the Winnipeg General Hospital, Winnipeg. Pp. 1047; 416 illustrations and 8 colored plates. Second edition thoroughly revised. Philadelphia: Lea & Febiger, 1934. Price, $10.00.

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PROGRESS
OF
MEDICAL SCIENCE

THERAPEUTICS

UNDER THE CHARGE OF
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INDICATIONS AND DANGERS OF THE USE OF BARBITURIC ACID DERIVATIVES.

SOME 30 years ago Fischer and von Mering[1] established the fact that while barbituric acid, a derivative of urea and malonic acid, is physiologically relatively inactive, the substance obtained by replacement of the two hydrogen atoms by ethyl radicals is a powerful hypnotic in animals and in man. Since this discovery a large number of other barbituric acid derivatives have been prepared by replacing one or both atoms by alkyl, cyclic and other radicals. Partly through their beneficial effects in certain conditions and partly through the zeal of the manufacturing houses these substances, introduced under various trade names, have become widely used in different branches of medicine. Veronal, luminal, ipral, amytal, allonal, dial, pernocton, somnifen, nembutal, and evipan are but a few of the trade names of the more commonly used barbituric acid derivatives. The barbituric acid derivatives are certainly among the most widely used drugs today. Not only are they popular as sedatives and hypnotics, but they are also used by some as anesthetics. The literature on the subject is voluminous and cannot be covered in a short review. Most of the contributions are characterized by claims of the low toxicity and relatively high hypnotic and analgesic action of the specific derivative discussed. Usually the popularity of such a preparation, reached mainly through direct and indirect advertising, wanes as a result of the personal experiences of physicians or of a more effective advertisement of a new preparation.

Although the main action of the various barbituric acid derivatives is the same, certain definite advances, particularly with reference to the persistence of action and the elimination of certain undesirable side

actions, have been made in recent years. The *chemistry* and the corresponding trade names of the most frequently used preparations have been discussed recently by Collins and Leech.[2] Among the numerous studies attempting to compare the chemical structure with the *pharmacologic action,* those of Dox and Hjort[3,4] are of particular interest. The relative anesthetic value was highest in the ethyl-iso-butyl, the ethyl normal butyl, the ethyl-iso-amyl and the ethyl normal hexyl barbituric acids, as compared with a large number of other members of the series. In the pharmacologic evaluation of the barbituric acids these authors have pointed out a number of other qualities in addition to the index of the minimal effective and minimal fatal doses. In the estimation of the minimal fatal dose, the time element is also of importance. The absolute amount of the minimal lethal dose of the various derivatives varies considerably, without necessarily altering the therapeutic efficacy of the drugs. The implication of this fact is often not appreciated by physicians.

Among the various types of pharmacologic studies the problem of the *excretion* of the barbituric acid derivatives bears directly on the clinical application. The chemical methods used in the identification and quantitative measurements of the barbituric acids are described in a recent article by Koppanyi, Murphy and Krop.[5] As early as 1910 Bachem[6] found that as high as 90% of diethyl barbituric acid (veronal) can be detected in the urine following the subcutaneous administration of small doses. Except in a few publications, the high percentage elimination through the kidneys has been confirmed repeatedly. Koppanyi, Murphy and Krop[5] found that in men, dogs and cats from 42 to 91% of barbital is excreted in the urine, whereas in fowl only 28.4%. Diuretic measures did not increase the rate of excretion or the total excretion of barbital. The concentration of barbital in the blood showed a sharp decline during the first 2 hours and then dropped slowly. The former is due to fixation by the organs; the latter to renal elimination. Bilaterally nephrectomized dogs failed to recover from barbital anesthesia. Estimation of barbital in various organs has indicated that the skeletal muscles and the kidneys contained particularly large amounts of the drug.

Next to the relative toxicity of the drug, its *persistence of action* is of primary consideration from the point of view of the clinic. On the whole, a barbiturate that possesses the least hypnotic and analgesic effect and has the longest persistence of action is the least desirable. Eddy[7] has found that among the more commonly used members of the series ethyl-iso-propyl barbituric acid is, for this very reason, undesirable. Of the substances with relatively high analgesic and hypnotic effect, but with a short duration of action, cyclo-hexenylmethyl-N-methyl-barbituric acid (evipan) is of special interest. This substance has been described recently by Weese.[8] Ten minutes after an intravenous narcotic dose the animals begin to awaken, and in from 30 to 60 minutes they have apparently completely recovered. The rapid detoxication of this barbituric acid derivative has been confirmed this year by the pharmacologic studies of Kennedy and Narayana.[9] Numerous workers have reported on the other pharmacologic effects of the barbituric acid derivatives. Most of the substances tested produce slight or no fall in arterial blood pressure, even in complete anesthesia. Cer-

tain phases of the carbohydrate metabolism are usually disturbed. Slowing of the respiration is induced. The effect on the gastro-intestinal canal is not prominent.

In *clinical use* the barbituric acids are usually administered by mouth, but some preparations can also be given through subcutaneous, intramuscular and intravenous routes. The latter method has become widespread particularly since 1924, when Dujol and Clément[10] advocated the intramuscular and intravenous use of somnifen in obstetrics, and Fredet and Perlis[11] used the same drug for the alleviation of pain in surgical operations. On the Continent such a use of the barbituric acids in surgery spread rapidly. In America this procedure was encouraged mainly by Zerfas, McCallum, Shonle, Swanson, Scott and Clowes.[12] who in 1929 reported on the induction of anesthesia in man through the intravenous administration of the iso-amyl-ethyl barbiturate (sodium amytal). The indiscrimate advocacy of the intravenous use of the barbituric acids has led to numerous serious and fatal accidents in this country and abroad. Simultaneously with the initial spread of the intravenous use of the barbituric acids, Weiss[13] called attention to the potential dangers of such an application. He advocated that the intravenous anesthetic doses should be regarded as potentially dangerous, particularly in surgery, and that their use should be restricted mainly to emergencies such as acute convulsions in eclampsia, epilepsy and cerebral vascular accidents. In severe cases of poisoning due to local anesthetics, in tetanus, and in persistent hiccough, their use was regarded as justified. The Council on Pharmacy and Chemistry of the American Medical Association in a recent report[14] reiterated its earlier warning against the indiscriminate intravenous use of the barbituric acids.

The most useful and widespread application of the barbiturates is in the field of sedatives and hypnotics. Notwithstanding the extensive literature on the subject, it is still impossible to formulate definite conclusions as to the relative merits of the various members in this respect. The use of the barbiturates has also been advocated in surgery, obstetrics and psychiatry, as well as in the treatment of convulsions of varying etiology, of tetanus, and of strychnin and local anesthetic poisonings.

For *surgical anesthesia,* they have not proved to be efficient. The reason for this is that the pharmacologic properties of all the members of the series indicate that the analgesic effect is not so great as that of some of the volatile anesthetics. The anesthetic dose is a relatively high percentage (50 to 70%) of the fatal dose. Weiss,[13] from observations on animals and on patients who took barbituric acids with suicidal intent, claims that man is more sensitive to the toxic effects than are animals, and that 23 to 37% of the fatal dose is required to induce sleep, moderate muscular relaxation and partial anesthesia. He has pointed out that pain, sympathetic excitement, worry and fever act antagonistically to the effect of the barbituric acids; where as cerebral depression is synergistic and therefore makes the patients susceptible to the depressant effect. Such an acute depression in the course of a severe operation with possible complications represents a potential danger if non-volatile anesthetics with long persistence of action, such as the barbituric acids, are used. Another danger in the long persistence

of action of the barbituric acids is from postoperative complications, particularly pneumonia. Today the barbituric acid derivatives are used mainly as preoperative and basal anesthetics, orally administered, and as such they are apparently of distinct value. Recently Bogan[15] has reported a study on the comparative adaptability of pernocton, avertin and pentobarbital sodium for basal anesthetics, and concludes that moderate doses of the basal drug are best. He prefers pentobarbital to pernocton. Bogan rightly emphasizes the increased need for postoperative care of the patient if non-volatile basal anesthetics are used. Axelrod[16] reports on the use of allyl-iso-propyl barbituric acid (allurate) as a premedication agent.

We have previously referred to the clinical advantages of cyclohexenylmethyl-N-methyl-barbituric acid (evipan) because of the short duration of its action. Since 1933, when Holtermann[17] first reported his clinical experiences with its intravenous use in gynecology and obstetrics, numerous reports have emphasized this property. Its use is therefore advocated in short surgical procedures. Buerkle-de la Camp[18] has used this anesthetic both as a basal and as a sole anesthetic in some 500 cases. Following the intravenous administration of from 4 to 7 cc. of the drug the patient falls to sleep without preceding restlessness. For anesthesia 9 cc. or more is usually required. Young patients have tolerated as high a dose as 22 cc. Most patients awake from 10 to 30 minutes after the administration of an anesthetic dose. In case restlessness is present or the operation is prolonged, $\frac{1}{2}$ to 1 cc. is reinjected every 5 to 10 or 15 minutes. Although these favorable claims were made only a year ago, certain warnings have appeared already. Jarman and Abel,[19] on the basis of experience in 100 cases, consider evipan a useful addition to surgical armamentarium, but claim that its use is contraindicated in feeble and toxic cases, and in the presence of liver disease. It should be administered only by expert anesthetists. In case respiratory embarrassment occurs, carbon dioxid and oxygen mixtures should be administered. Landau and Wooley[20] report on a prolonged and late toxic reaction in a patient following the intravenous use of 10 cc. of sodium evipan. Mörl,[21] a few months after the introduction of evipan, reports a fatal case and mentions three additional fatalities, one transient cardiac standstill, and 2 cases of collapse, the latter occurring after the administration of such small doses as 2 to 3 cc. These reports of toxic reactions indicate that while evipan is of distinct interest because of the short duration of its action, and under special indications may be of distinct usefulness, its intravenous administration for anesthesia is not without danger.

Recently, renewed attempts have been made to use the barbituric acids for the relief of pain and for the induction of amnesia *in labor*. Averett[22] advocates the combined use of nembutal and scopolamin when labor is definitely established. Six grains of nembutal are given by mouth and 1/100 gr. scopolamin hydrobromid subcutaneously. The average duration of analgesia in 160 cases was $5\frac{1}{2}$ hours. No change in the respiration was noted. The blood pressure dropped 5 to 10 mm. The frequency and severity of uterine contractions were not interfered with. The first stage of labor either was not altered or was of shorter duration. The second and third stages were unchanged. In 110 cases complete amnesia was present, and in 42 cases there was some recollection. Maternal and fetal mortality did not occur. McGuinness[23] has

used nembutal because of the relatively short duration of its action in 140 cases of full-time confinement. A patient weighing 160 pounds received an initial dose of 6 gr. by mouth, followed by a second dose of 3 gr. within 3 hours, and by successive doses of 3 gr. every 2 or more hours until delivery. The capsules were administered on an empty stomach, with warm water. Rectal administration is also feasible. Fifteen minutes after the first dose the patient became drowsy and in 30 minutes she was sleeping between pains. During uterine contraction there were usually groaning, restlessness and partial awakening. Postoperative nausea and vomiting were not increased. Little or no interference with the course of labor was observed. Irving, Berman and Nelson[24] report their extensive experiences in the Boston Lying-In Hospital on the comparative efficacy of pantopon and scopolamine, pantopon and rectal ether, pernocton, sodium amytal, scopolamine and pentobarbital, scopolamine and sodium amytal, rectal ether and pentobarbital, and rectal ether, pentobarbital and paraldehyd. In each series, 100 cases were used with the exception of the sodium amytal and scopolamine series, which consisted of 160 patients. Pentobarbital and scopolamine was considered the most effective of any of the medications used. Absolute loss of memory was shown by 86% of the patients; incomplete amnesia by 14%. The only side effect was restlessness, which was frequently present. They advise against the use of pantopon and morphin during labor, as they delay the initial breathing of the baby.

The therapeutic induction of prolonged sleep by means of barbituric acids in patients with *psychosis* dates back to 1922, when Kläsi[25] advocated the beneficial effect of the repeated intravenous use of somnifen in certain psychoses. It has been claimed that such a prolonged sleep may aid in interrupting the course of a psychosis and so hasten recovery. Müller,[26] in 1925, reviewing the literature and his personal experiences on the intravenous use of somnifen in certain psychoses, mentions 15 fatalities as well as severe non-fatal intoxications during the treatment of 311 patients. The immediate cause of death was circulatory failure in 5 instances and pneumonia in 6; in 4 patients other etiologic factors were present, but somnifen was a contributing cause of death. There are two recent reports on the use of barbiturates in neuro-psychiatric conditions. Wagner,[27] summarizing his general clinical experiences, warns that if the drugs are given over a long period the histologic changes produced by the administration of large doses may lead to permanent functional impairment. Lorenz, Reese and Washburne[28] report on physiologic observations during intravenous sodium amytal medication in 350 patients with psychosis: an average of $9\frac{1}{2}$ gr. (14.3 cc. of a 5% solution) were required to obtain complete narcosis. The functional group of psychoses required a somewhat larger dosage than the organic group. Because of the great instability of the blood pressure in the involutionary group greater caution was required in this group.

The problem of *addiction* to barbituric acids has repeatedly been discussed in the literature. Gillespie,[29] summarizing the evidence, denies its occurrence. (The reviewer is inclined to agree, if addiction is restricted to habits associated with withdrawal symptoms. Morphin and cocain addicts, on the other hand, in case of insufficient supply or lack

of supply, often substitute barbituric acids. Psychologic habit formation to the barbituric acids is not uncommon.)

In view of the widespread clinical use of the barbiturates, as well as their recent rather frequent use with suicidal intent, *poisoning* is relatively common. The most frequent manifestations of intoxication, as is well known, are coma, disturbances of the heart regulation, and tendency to vasomotor collapse. In a recent review of the subject Gillespie[29] found no record in which barbiturates, either in single or in repeated smaller therapeutic doses, caused death in the absence of complicating factors. He has estimated that the ratio of safety with smaller therapeutic doses is 1 to 5 with veronal and 1 to 3 with luminal. Carrière, Huriez and Willoquet[30] summarize the histologic changes observed in man and in rabbits following fatal barbituric poisoning. Degenerative changes are described in the liver and kidney parenchyma, as well as disintegration of the cells of the central nervous system. Congestion in the lungs, with tendency to bronchopneumonia, was observed. A review of the literature up to 1929 is also presented by Lundy and Osterberg.[31]

That cutaneous rash may follow the use of even small amounts of certain barbiturates has been known since 1903.[32] The recent interest in the relation of allonal to agranulocytosis has also raised the question of whether cutaneous hypersensitivity is caused by allonal (mixture of allyl-iso-propyl barbituric acid and amidopyrin and allurate [allyl-iso-propyl barbituric acid]). Unger[33] reports a patient who, after the ingestion of only one tablet of allonal, experienced swelling of the eyelids, cheeks and lips. Blotches appeared on the forehead, palms and backs of the hand. Crohn[34] has reported a case with repeated attacks of urticaria, and scrotal and genital edema after taking allional (a preparation similar to allonal). In a case reported by Loveman[35] exacerbation of an eruption was produced by allonal. Separate administration of allurate and amidopyrin showed that the cutaneous sensitivity was due to the barbituric acid and not to amidopyrin. Allyl-iso-propyl carbamid and numerous other barbiturates did not induce skin lesions. Other drugs producing fixed eruptions, such as phenolphthalein, antipyrin and amidopyrin had no effect. Passive transfer to hypersensitivity was unsuccessful. Patch, intracutaneous and scratch tests were all positive to allonal and allurate in previously active areas, but produced no reaction in normal skin areas. Thus in this case allyl-iso-propyl barbituric acid was definitely responsible for skin sensitivity.

Madison and Squier[36] claim that the "benzene chain derivatives" are probably responsible for primary granulocytopenia. From their data, however, one cannot ascertain whether the barbituric acid in addition to amidopyrin plays any rôle. Watkins,[37] reporting 32 cases of primary granulocytopenia, has observed 5 patients who had taken iso-amyl-ethyl barbituric acid or its sodium salt prior to the onset. All these patients died. Four patients with fatal outcome had taken sodium ethyl-methyl-butyl barbiturate. Two patients, one of whom died, had taken phenobarbital. As acknowledged by the author, the presented data simply suggest the possibility that certain individual idiosyncrasies of the white blood cell forming apparatus exist. Whether the barbituric acid derivatives can be directly responsible for agranulocytopenia is therefore not yet settled.

The *treatment* of severe barbituric poisoning, until very recently, has been unsatisfactory. The most promising recent method of treatment is based on strychnin and barbituric acid antagonism. Haggard and Greenberg[38] have shown in 1932 that phenobarbital sodium controls strychnin convulsions in rats and dogs. Animals have survived 5 times the fatal dose of strychnin. That the antagonism is a reversible one was shown by the fact that animals receiving 3 times the fatal dose of phenobarbital sodium have been saved with strychnin. Kempf, McCallum and Zerfas[39] have treated 11 cases of strychnin poisoning with sodium amytal and sodium pentobarbital, given intravenously, and claim that these substances were life-saving measures. Successful treatment of barbituric acid poisoning with massive doses of strychnin has been reported recently in France. Bertrand-Fontaine and Claass[40] have reported the case of a young woman who ingested 17 gm. of veronal and after being in coma received a total of 39 centigrams of strychnin by vein in 64 hours. A solution containing 3 mg. per cubic centimeter was used. Every hour during the day and every 2 to 3 hours at night doses of 9 to 15 mg. of the sulphate salt were given. Manifestations of strychnin poisoning were not observed and recovery followed. Eschbach[41] reports a case with severe phenobarbital poisoning receiving 26 mg. of strychnin by vein within 2 hours. Instantaneous improvement with ultimate recovery followed. Denéchau and Bonhomme[42] describe a female patient of 29, who had taken 6 gm. of phenobarbital, receiving a total of 48 centigrams of strychnin before recovery. Laignel-Lavastine and Bidou[43] describe recovery in a case with severe dial poisoning. The patient was in coma for 30 hours when an initial intravenous dose of 20 mg. of strychnin was given, followed by a second dose of 10 mg. in 1 hour, and then 10 mg. every 2 hours and 2 injections every 3 hours. The last injection was 10 mg., 10 hours later. The patient recovered. Additional cases of the strychnin treatment of barbituric acid poisoning have been reported.[44,45,46]

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TOXIC REACTIONS FOLLOWING THE CLINICAL USE OF ALPHA-DINITROPHENOL (1-2-4).

THE pharmacologic properties and therapeutic application of dinitrophenol have recently been discussed in this column.[1] Without entering into the rationale of weight reduction through elevation of the metabolism rather than through regulation of the diet, it has been concluded that while final judgment on the therapeutic value of dinitrophenol cannot as yet be expressed, the substance deserves further trials in therapy. The most recent reports on toxic and fatal responses now justify a definite warning, and the evidence indicates that the administration of dinitrophenol, even in the therapeutic doses advocated in the past, may at times be dangerous. It was pointed out in the first review that the reported fatalities, with but one exception,[2] have resulted from voluntary or accidental overdosage. In a recent medicolegal case reported from England, death in a young dancer also resulted from overdose.[3] Poole and Haining[4] have described a case of rapidly fatal outcome in a young woman who, without the advice of a physician, took dinitrophenol. Autopsy revealed tubular degeneration of the kidneys and separation of liver cells in the lobules. The data given definitely indicate that the dosage was high, being several times the average daily dose. Nevertheless, the authors consider that the amount taken was within the presumed limits of safety; hence they look upon this fatality as an example of allergic idiosyncrasy.

Frumess[5] studied the nature of the toxic skin reaction which developed in a female patient 26 years of age, who had an allergic history. Seventeen days after she had started taking 100 mg. of dinitrophenol twice daily, she developed generalized giant urticaria with angioneurotic

edema. The allergic nature of the skin reaction was demonstrated by the passive transfer of the antibodies in the patient's serum to a normal subject, and their subsequent demonstration by the Prausnitz-Küstner method. Local and focal response of the skin of the patient to applications of the drug by the scratch method suggest the drug as the cause of the reaction. The author states, without giving evidence, that skin eruption occurs in an appreciable percentage (at least 7%) of those to whom dinitrophenol is administered. He also states that from a theoretical viewpoint it is dangerous to resume the use of the drug after a skin reaction has subsided. Matzger[6] has studied, with negative results, the problem of skin sensitivity to sodium dinitrophenol by means of the patch, scratch and intradermal methods in 157 subjects. Three of these patients later showed a severe skin reaction to dinitrophenol. In a patient who showed a severe skin reaction to dinitrophenol, passive transfer of sensitivity could not be demonstrated. He concludes that skin tests will be of no value in predicting skin sensitivity. Jackson and Duvall[7] report a severe degree of cutaneous reaction in a 42-year-old woman who took 100 mg. of dinitrophenol 3 times daily for 10 days. On the 11th day a slight rash appeared on the chest. On the 14th day a severe erythematous papular rash appeared over the entire surface of the body, including the scalp. The hands and feet swelled to twice their normal thickness, and the eyelids were swollen shut. The height of the symptoms was reached on the 4th day after the appearance of symptoms. In 8 days the improvement was considerable.

Among the cases of neutropenia reported by Hoffman, Butt and Hickey,[8] there was 1 patient who took 100 mg. of dinitrophenol 4 times a day for 2 weeks. This patient recovered after Roentgen ray and pentnucleotide therapy. Bohn[9] reports a case of agranulocytic angina in a girl of 19, who over a period of 4 months took 21.8 gm., usually starting by taking one capsule 3 times a day for 2 weeks, then doubling the dosage for 1 or 2 weeks until warmth, perspiration, fatigue, sore throat and pruritic maculopapular eruptions appeared. After ingestion of the drug was stopped these symptoms disappeared within 2 to 3 weeks, after which she resumed taking the drug. This patient recovered after treatment. Davidson and Shapiro[10] report the occurrence of neutropenia with progressive pain with swelling in the gums and submaxillary glands. The patient subsequently recovered after a dose of 6 gm. in 20 days. Sidel[11] observed a 26-year-old woman who, after taking 100 mg. 4 times a day for 14 days, developed pain in the epigastrium. Severe jaundice indicated a hepatitis, which cleared up slowly in the course of over 8 weeks.

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RADIOLOGY

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PULMONARY TUBERCULOSIS.

In the opinion of Sampson and Brown, thoracic surgery has attained the advanced position it has today solely because of the precise diagnosis of the extent of the pulmonary lesion which is made possible by roentgenologic study. Roentgenograms of the lung may be likened to pulmonary biopsy, and although histopathologic study of any given lung is limited of course to disclosure of a single state, in a series of roentgenograms one has the diagnostic equivalent of serial biopsies of lesions in a state of flux. Such studies have greatly helped to banish ennui from sanatoriums.

Physical methods of pulmonary diagnosis cannot safely be neglected. However, primary infection in infancy and childhood that produces a small patch of bronchopneumonia cannot be diagnosed by physical signs; the condition is rarely detected save by accident, and roentgenologically it can be detected only at such time as it has apparently become healed and calcified or ossified. The same thing is true of the associated changes in the tracheobronchial lymph nodes; such changes also entirely escape detection by physical examination and are not seen roentgenologically until such time as they project their shadows into the high light of the bronchus or into the normal roentgenologic field. D'Espine's sign has been shown by roentgenographic study to be of no value. The importance of the discovery of the primary infection is attested by the thousands of dollars spent during the last one or two decades for roentgenologic investigation, which alone is capable of localizing in the lung an infection suggested by a positive tuberculin test. Physical signs tell little of what happens in tuberculosis of the lungs during that period when the disease exacts its least toll of human life, the interval between primary infection and the development of definite pulmonary tuberculosis.

Sampson and Brown felt that roentgenology has given some proof that the adult type as a rule does not arise directly by extension from the primary lesion. If by the age of 23 there are no parenchymatous changes in the lung suggestive of pulmonary tuberculosis, only in rare instances will pulmonary tuberculosis develop. No child should be allowed to leave school, particularly high school, until roentgenologic examination of the thorax has been made. In Sampson and Brown's experience with 4000 examinations, conducted over a period of 7 years, only 7 of 79 children with parenchymal lesions had definite physical signs on examination. The roentgenogram revealed that the usual site

of beginning, clinical pulmonary tuberculosis was in the upper lobe below the clavicle. Of 280 patients with minimal pulmonary tuberculosis, râles were present in the apex in 27%, whereas a definite parenchymatous lesion was revealed roentgenologically in more than 99%. Hemoptysis was as frequent as râles (26%), whereas pleuritic effusion occurred in 12% of cases. Bacilli of tuberculosis were found in 35%. In a series of 1004 consecutive cases studied, there were no patients with definite physical signs and a negative roentgenogram. In 19 cases the physical signs suggested greater extent of the lesion than did the roentgenogram. In 211 cases the extent of the lesion appeared to be the same by both methods. In 361 cases the roentgenogram revealed more extensive disease than was inferred from the physical signs. In 396 cases the roentgenogram gave definite evidence of pulmonary tuberculosis, whereas the physical signs were practically normal. In 392 cases in which a cavity was revealed in the roentgenogram, physical signs of the cavity were present in only 58 (15%). Sampson and Brown placed great significance on the roentgenogram in determining the prognosis of pulmonary tuberculosis. Willis asserted that pneumonic consolidation that involves a comparatively large portion of a lobe, or even an entire lobe, is particularly prone to appear among children. It is the general impression that these consolidated areas definitely occur more frequently than would be expected if they were caused by the pneumococcus, that is, that they are encountered more commonly among tuberculous patients than among people in general. Usually the consolidated areas under consideration have been attributed to one of the following causes: atelectasis, edema, pneumococcal pneumonia, nonspecific pneumonia in tuberculous individuals, known as "epituberculosis," and tuberculous pneumonia. The term, atelectasis, is loosely used by some; certain physiologists and experimental physiologists assert that there can be no true atelectasis, short of that involving an entire lobe, unless it is brought about by the diseased alveolar walls which act as barriers to the air in neighboring air spaces. Physical examination is usually quite different in pneumonic consolidation and in massive collapse, and is highly characteristic in each condition. Willis felt that edema has little to do with the formation of the characteristic roentgen shadows. Pneumococcal pneumonia occurs only rarely among patients in sanatoriums.

That a peculiar nonspecific pneumonic consolidation may occur in tuberculous patients (and in these only) is the contention of Eliasberg and Neuland, who gave the affection the name, epituberculosis. The only criteria for ordinary pneumonia which these consolidated areas offer are the physical signs of consolidation. Several points make the diagnosis of tuberculosis highly probable if not mandatory. These are: (1) the long duration, (2) the lack of stormy symptoms, (3) the necessary presence of tuberculous infection, as evidenced by the tuberculin reaction, (4) the presence of bacilli of tuberculosis in the sputum, as demonstrated in numerous instances, (5) the histologic appearance of excised pulmonary tissue in a clinical case, and (6) the reappearance of the condition in children after injection of tuberculin. The considerable volume of experimental work of others and their own experimental data indicates that tuberculous pneumonia may be induced in experimental animals. This disease frequently undergoes resolution, as is

evidenced by serial roentgenograms and at necropsy. It is clear that this pneumonia of animals is specifically tuberculous in nature. It is likely that such specific pneumonic processes are very similar to, or identical in nature with, clinical pneumonic consolidations that occur in tuberculous individuals, and that each is the product of the exudative, allergic reaction of an animal organism which is sensitive to bacilli of tuberculosis and tuberculin.

Allison and Medelman presented a study based on observations of a series of thoracic roentgenograms of tuberculin-tested children made over a period of years. The series embraced more than 10,000 children many of whom were reëxamined roentgenologically over a period of 10 years. Allison and Medelman's classification of first infection tuberculosis in childhood is: (*A*) known infection with no demonstrable lesion, (*B*) uncalcified tuberculosis of the primary pulmonary or childhood type, (*C*) calcified tuberculosis of the primary pulmonary or childhood type, (*D*) adult type tuberculosis with or without a demonstrable primary focus. In considerably more than half of the cases in Group A in which the Mantoux reaction was positive, no lesions in the thorax attributable to tuberculosis were demonstrated. In Group B the primary focus is situated in any part of either lung and is in the form of tubercles. Occasionally it may be bilateral, its size varying within wide limits. In unfavorable cases the primary focus may break down with formation of a cavity. Various complications caused by the dissemination of the tubercle may occur. Allison and Medelman have observed cavitation, miliary tuberculosis, bone tuberculosis, and tuberculous enteritis which developed during the evolution of an uncalcified pulmonary lesion of the first infection type. These complications, however, were extremely rare. The typical roentgenologic appearance is that of a homogeneous, dense opacity which involves a lobe, or a roughly triangular portion of a lobe with the base of the triangle toward the periphery. Quite frequently the hilar and mediastinal lymph nodes draining this region can be visualized as a separate lobulated mass. The density of the infiltration decreases, and finally completely disappears, at about the time the calcified deposits fuse into one or more dense Ghon tubercles. As regression of the parenchymal lesion occurs, calcium is deposited in the involved lymph nodes. The most frequent lesion simulating resolving parenchymal tuberculosis is pneumonia. If the roentgenologist cannot be sure of the differential diagnosis at the original examination, he may take another roentgenogram in a week or 10 days; if the lesion is unchanged, the diagnosis is obvious. It is very important from a clinical standpoint to differentiate adult and childhood types. This is done by: (1) the well-known appearance of the adult type of infection, usually in the upper half of the lungs; (2) previously existing calcification of a former primary infection; (3) the presence of enlarged nodes in the childhood type and their absence in the adult type, and (4) if necessary, prolonged observation. Tuberculosis of childhood has a tendency to improve and to calcify, whereas adult tuberculosis tends to increase without calcification.

Primary tuberculous involvement of the tracheobronchial lymph nodes may occur without a demonstrable pulmonary focus. The diagnosis in such cases depends on actual visualization of a rounded density or lobulated mass extending into the parenchyma of the lung from the

hilus or mediastinum, or both. From infancy to the age of 18 years it will not be seen in more than 4 or 5% of all cases. About 25% of the children with a positive Mantoux reaction fall into Group C. The discovery of calcified deposits gives definite evidence of the tuberculous nature of the lesion, except in rare instances. The adult type of tuberculosis occurs on reinfection of those children who have previously been sensitized by a childhood type of infection. At least 50% of all children with the adult type of tuberculosis have it superimposed on a demonstrable childhood tuberculosis.

Pinner stated that the hematogenous (nonmiliary) type of pulmonary tuberculosis seems to be little known. On account of its atypical manifestations, it is frequently not diagnosed. It has been described in the literature quite frequently, mostly in the form of reports of cases and under a great variety of names. A discussion of the literature would not particularly help to clarify the matter as it stands. Of Pinner's 28 reported cases, 14 came to necropsy. Roentgenologically the disease is characterized by multiple, small foci which are usually more or less symmetrically distributed throughout the fields of both lungs. The distribution may be more or less even, or it may be limited to certain parts of the lungs, usually to the upper parts. The clinical symptoms and physical findings are often in great disproportion to the amount of roentgenologically demonstrable involvement. The further development of these lesions reveals certain well-defined characteristics that distinguish them clearly from bronchogenic tuberculosis. This type is assumed to be due to a hematogenous spread, or to repeated ones, for the following reasons: (1) the more or less even distribution of the lesions, (2) the frequent absence of older pulmonary foci from which a bronchogenic spread could have occurred, and (3) the frequent association of extrapulmonary lesions with the pulmonary lesions. The major morbid processes take place within the interstitial structure of the lung. These patients have little sputum and rarely with bacilli; the appearance of bacilli in the sputum indicates small ruptures into the canalicular system of the lung.

Watkins, discussing the healing of cavities in pulmonary tuberculosis observed roentgenologically, remarked that it was a clinician who asserted that only 60% of cavities were found by physical examination whereas 95% of them were revealed by roentgenologic examination. The majority of critical observers accept as substantially correct Graeff's statement (1921) that the development of a pulmonary cavity is a death sentence for the unfortunate patient. This statement is subject to many exceptions. A tuberculous patient with a cavity as large as 1 inch in diameter has an average life expectancy under treatment of only 1 year. Probably half of the patients can be healed by simple or modified rest in bed. For another fourth the cavity can be closed by pneumothorax. The remaining fourth will require the assistance of a thoracic surgeon for such procedures as phrenicectomy, intrapleural and extrapleural pneumolysis, and thoracoplasty. Roentgenologic study offers the only certain means of determining whether a cavity is enlarging or healing under treatment.

Bruck, in describing a round foci type of pulmonary tuberculosis, stated that Straub (1932) wrote a comprehensive article analyzing all cases reported up to that time. Straub found no reference to this type

of tuberculosis in the American literature. Six to 8 isolated cases were reported in the German literature and Straub described 10 cases seen at his clinic. This form of tuberculosis occurs as round foci in a thorax that has other definite and characteristic lesions, or these foci may be the only evidences of the disease. The lesions can be detected only by Roentgen rays, they are usually quiescent, and many times they produce no symptoms but are often detected accidentally during the course of other roentgenologic studies. Roentgenographically, over a period of years, the lesions do not appear to have undergone any definite change. Clinically, most of the patients are afebrile, have no constitutional reactions, and feel no discomfort. In Bruck's case the sputum was positive for bacilli of tuberculosis. On biopsy, tuberculosis of the right vocal cord was found. A small minority of the cases reported clinically gave evidence of activity.

Murphy, in discussing bronchography as an essential and safe adjunct in the study of pulmonary tuberculosis, reviewed the history of the application of bronchography to the study of bronchiectasis and pulmonary tuberculosis and described the technique employed. The study combined roentgenoscopy and roentgenography. Ninety-nine injections of lipiodol were made in cases of pulmonary tuberculosis in which there were no major complications. Bronchial dilatation was observed in 60% of 65 cases, ranging from infiltrating to fibrocavernous lesions. Variability in the association of bronchial dilatation and tuberculosis was noted. Bronchial dilatations of all types and extent, which could not be distinguished from parenchymal lesions in the ordinary roentgenogram, were clearly defined in the bronchogram.

Neuhof considered bronchography an essential measure for the precise localization of the lesion and delineation of the part of the pathologic process in pulmonary tuberculosis, when surgery is indicated, just as experience has taught it is in pulmonary abscess. When cavities are formed, a small fluid level has been the maximal direct evidence of those in the upper lobe· the bronchogram adds indirect evidence by delineating the disposition of the bronchi and bronchioles around the site of cavitation, usually about its lower circumference, outlining its situation and shape. Areas of rarefaction in the roentgenogram have been identified as cavities in the bronchogram. Bronchiectasis in the pulmonary parenchyma about the cavity can usually be differentiated. Bronchiectasis in the lower lobe is often revealed as a grossly abnormal bronchial tree, whereas in the roentgenogram it appears only as a slight abnormality. Bronchography is of great value in estimating the degree of fibrosis and retraction in the tuberculous lobe; it may avoid some futile operations on the phrenic nerves and not a few ineffective pneumothorax treatments. It has also been found useful in the demonstration of the results of the mechanical treatment of pulmonary tuberculosis.

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Glass, in a series of illustrations, outlined the bronchopulmonary segment with special reference to putrid pulmonary abscess. In its primary evolution, an abscess involves definite and circumscribed regions of the lung. These regions are subdivisions of pulmonary lobes and constantly possess a definite shape, size, and position in the thoracic cavity. Each is composed of a bronchus and its associated alveolar tissue. The bronchus is one of the main divisions of a lobar branch, and each segment is a potential zone of infection through aspiration. Each segment is named according to its position in the thoracic cage and the pulmonary architecture. The postero-anterior roentgenogram affords the clearest view of the lung and always reveals shadows of abscesses to the best advantage.

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In clinical roentgenography, if the diaphragm is examined at expiration as well as at inspiration, elevation of the diaphragm on the side of the lesion should occur in atelectasis at both phases of respiration, whereas in pneumonia it occurs, if at all, at inspiration only. Focal atelectasis presents scattered mottlings, cloudings, and streaks which correspond to the positions of the individual foci of alveolar collapse; the ground-glass sign is absent. Focal atelectasis occurs in pure form most frequently in the compressive and congenital types of the disease.

The markings tend to be arranged in lines radiating from the hilus. The majority of cases of postoperative atelectasis are of the focal form. The Roentgen shadow of a pneumonic area of lung is practically always heterogeneous in composition because of the air which is scattered through the lesion; even at the height of the disease careful scrutiny discloses faint cloudings or mottlings rather than a completely uniform and ground-glass shadow. The same applies to tuberculosis. Hemorrhagic infarction is almost always heterogeneous in consistency owing to the presence of smaller or larger amounts of air in the tissues. Neoplasms present the ground-glass sign, but in pure form they are readily distinguished from massive collapse by the absence of the environmental displacement that characterizes the latter disease. In extrapleural masses, the viscera adjacent to the lungs are either not displaced at all or are displaced in a different direction than in atelectasis. When massive atelectasis and other consolidative disease occupy the same portion of the lung, the ground-glass superimposed shadow obliterates all marks of the other lesions.

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ORIGINAL ARTICLES.

CHRONIC CONGESTIVE SPLENOMEGALY AND ITS RELATIONSHIP TO BANTI'S DISEASE.

By Ralph C. Larrabee, M.D.,
CONSULTING PHYSICIAN, BOSTON CITY HOSPITAL,
BOSTON, MASS.

When a patient is admitted to the wards of a hospital with an enormous spleen, anemia with leukopenia and perhaps a history of gastro-intestinal bleeding, the tentative diagnosis is likely to be Banti's disease. Many such cases have been treated—and with much success—by splenectomy. If, however, the patient is a confirmed alcoholic, or if further research discloses evidence of cirrhosis of the liver or some other intra-abdominal abnormality, the splenomegaly is apt to be attributed to *that*. In the resulting doubt and confusion the patient will probably lose the benefit of an operation from which he might have obtained great relief. For there is a prevalent impression that only Banti's disease (and not splenomegaly due to liver cirrhosis) should be treated by splenectomy.

Banti's disease, though frequently diagnosed in the ward, is, if Banti's right to define the disease that bears his name is respected, extremely rare on the autopsy table. Strictly adhering to Banti's classical description,[1,2] the patient must have progressed through certain definite stages, the spleen must show certain and none too perspicuous histologic changes and, above all, there must be no obvious etiologic factor. So rare are the cases that fill all of these requirements, both positive and negative, that most of them emerge from the pathologic laboratory labeled cirrhosis of the liver or perhaps classed on some other equally definite etiologic basis. And the Banti pigeon-hole remains nearly, if not quite, empty!

of tuberculosis in the American literature. Six to 8 isolated cases were reported in the German literature and Straub described 10 cases seen at his clinic. This form of tuberculosis occurs as round foci in a thorax that has other definite and characteristic lesions, or these foci may be the only evidences of the disease. The lesions can be detected only by Roentgen rays, they are usually quiescent, and many times they produce no symptoms but are often detected accidentally during the course of other roentgenologic studies. Roentgenographically, over a period of years, the lesions do not appear to have undergone any definite change. Clinically, most of the patients are afebrile, have no constitutional reactions, and feel no discomfort. In Bruck's case the sputum was positive for bacilli of tuberculosis. On biopsy, tuberculosis of the right vocal cord was found. A small minority of the cases reported clinically gave evidence of activity.

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